PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/12, C07K 16/28, 19/00, C12N 5/10, 15/85, A61K 39/395 — A1

(11) International Publication Number: WO 95/27061

(43) International Publication Date: 12 October 1995 (12.10.95)

(21) International Application Number: PCT/US95/04228

(22) International Filing Date: 4 April 1995 (04.04.95)

(30) Priority Data:
08/222,616 4 April 1994 (04.04.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US
Filed on 08/222,616 (CIP)
4 April 1994 (04.04.94)

(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BENNETT, Brian, D. [US/US]; 1332 Oddstad Boulevard, Pacifica, CA 94044 (US). GOEDDEL, David [US/US]; 2115 Forestview Avenue, Hillsborough, CA 94010 (US). LEE, James, M. [US/US]; 705 Shelter Creek, San Bruno, CA 94066 (US). MATTHEWS, William [GB/US]; 560 Summit Springs Road, Woodside, CA 94062 (US). TSAI, Siao, Ping [-/US]; 519 Orange Avenue, South San Francisco, CA 94080 (US). WOOD, William, I. [US/US]; 1400 Tarrytown Street, San Mateo, CA 94402 (US).

(74) Agents: LEE, Wendy, M. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US).

(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

(57) Abstract

Agonist antibodies are disclosed which bind to the extracellular domain of receptor protein tyrosine kinases pTKs, and thereby cause dimerization and activation of the intracellular tyrosine kinase domain thereof. The antibodies are useful for activating their respective receptor and thereby enabling the role of the tyrosine kinase receptor in cell growth and/or differentiation to be studied. Chimeric proteins comprising the extracellular domain of the receptor pTKs and an immunoglobulin constant domain sequence are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to novel protein tyrosine kinase (pTK) genes, the proteins encoded by these genes, RNA nucleic acid sequences which hybridize to the genes, antibodies specific for the encoded proteins, chimeras of the proteins and methods of use therefor.

In particular, this application relates to agonist antibodies which are able to activate the tyrosine kinase domain of the receptor pTKs disclosed herein and pTK-immunoglobulin chimeras.

DESCRIPTION OF RELATED ART

Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases are enzymes that catalyze this process. Moreover, many act as growth factor receptors. The c-kit subgroup of receptor tyrosine kinases catalyze the phosphorylation of exogenous substrates, as well as tyrosine residues within their own polypeptide chains (Ullrich *et al.*, Cell 61:203 [1990]). Members of the c-kit subgroup include FLT/FLK (Fetal Liver Kinase), FGF (Fibroblast Growth Factor Receptor) and NGF (Nerve Growth Factor Receptor).

The *EPH* tyrosine kinase subfamily, Eph, Elk, Eck, Eek, Hek, Hek2, Sek, Ehk-1, Ehk-2, Cek-4 to -10, Tyro 1, 4, 5 and 6, appears to be the largest subfamily of transmembrane tyrosine kinases (Hirai *et al.*, Science 238:1717-1720 [1987]; Letwin *et al.*, Oncogene 3:621-678 [1988]; Lhotak *et al.*, Mol. Cell. Biol. 13:7071-7079 [1993]; Lindberg *et al.*, Mol. Cell. Biol. 10:6316-6324 [1990]; Bohme *et al.*, Oncogene 8:2857-2862 [1993]; and Wicks *et al.*, Proc. Natl. Acad. Sci. USA. 89:1611-1615 [1992]; Pasquale *et al.* Cell Regulation 2:523-534 [1991]; Sajjadi *et al.*, New Biol. 3:769-778 [1991]; Wicks *et al.*, Proc. Natl. Acad. Sci. USA. 89:1611-1615 [1992]; Lhotak *et al.*, Mol. Cell. Bio. 11:2496-2502 [1991]; Gilardi-Hebenstreit *et al.*, Oncogene 7:2499-2506 [1992]; Lai *et al.*, Neuron 6:691-704 [1991]; Sajjadi *et al.*, Oncogene 8:1807-1813 [1993]; and Maisonpierre *et al.*, Oncogene 8:3277-3288 [1993]).

Additional pTKs and agonist antibodies thereto are needed in order to further study growth and differentiation of cells, for use as therapeutic agents and for diagnostic purposes. Accordingly, it is an

object of the present invention to provide novel pTK genes, the proteins encoded thereby, antibodies specific for the encoded proteins, chimeras of the proteins and methods of use thereof.

SUMMARY OF THE INVENTION

The genes isolated as described herein are referred to, collectively, as "protein tyrosine kinase genes" or "pTK genes". The nucleic acid sequences of some of these genes, isolated as discussed herein, show significant homology with previously identified protein tyrosine kinases containing extracellular domains, which function as growth factor receptors (*e.g.*, pTKs of the c-kit subgroup). Some of the pTK genes have been shown to be present in both megakaryocytic and lymphocytic cells.

In particular, fourteen pTK genes have been identified. Two pTK genes, referred to as SAL-S1 and SAL-D4 were identified in megakaryocytic cells. SAL-D4 is related to the CSK family of intracellular pTKs and SAL-S1 is related to the FGF receptor family of pTKs. Five pTK genes, referred to as LpTKs, were identified in lymphocytic cells and have been shown to be present in megakaryocytes as well. One pTK gene, referred to as HpTK5, was identified in human hepatoma cells. Six pTK genes, referred to as bpTK genes, were found in human brain tissue.

The pTK genes, which are the subject of the present invention, were generally identified using two sets of degenerative oligonucleotide primers: a first set which amplifies all pTK DNA segments (SEQ ID NOS: 1-2), and a second set which amplifies highly conserved sequences present in the catalytic domain of the c-kit subgroup of pTKs (SEQ ID NOS: 3-4). The pTK genes identified in this manner are described below.

SAL-S1 is expressed in several megakaryocytic cell lines, but not in erythroid cell lines. The nucleotide sequence of part of SAL-S1 was obtained, revealing a sequence containing 160 base pairs (SEQ ID NO: 5). This isolated DNA fragment encoded an amino acid sequence (SEQ ID NO: 6) which exhibited significant sequence homology with known protein tyrosine kinases of the FLT/FLK family. The deduced amino acid sequence of SAL-S1 (SEQ ID NO: 32) contains 1298 residues.

SAL-D4, also expressed in megakaryocytic cells, is a DNA fragment containing the nucleotide sequence of 147 base pairs. (SEQ ID NO: 7). This isolated DNA fragment encoded an amino acid sequence (SEQ ID NO: 8) which exhibited significant sequence homology with known protein tyrosine kinases of the CSK intracellular pTK family.

The LpTKs, including LpTK 2, LpTK 3, LpTK 4, LpTK 13 and LpTK 25, are expressed in lymphocytic cells, as well as megakaryocytic cells. The nucleotide sequence (151 base pairs) of the LpTK 3 gene was obtained (SEQ ID NO: 11). The nucleotide sequences of the LpTK 2, LpTK 4, and LpTK 13 genes contained 149 base pairs (SEQ ID NO: 9), 137 base pairs (SEQ ID NO: 13), and 211 base pairs (SEQ ID NO: 15) respectively. LpTK 25 has a nucleotide sequence of 3120 b.p. (SEQ ID NO: 22). A full length gene sequence has been obtained for LpTK 2 (SEQ ID NO: 19) which contains 7607 b.p. Additional sequencing of LpTK 4 revealed a sequence of 404 b.p. (SEQ ID NO: 21).

The HpTK5 gene, expressed in human hepatoma cells, has a nucleotide sequence of 3969 b.p. (SEQ ID NO: 23).

Nucleotide sequences of the bpTKs, including bpTK 1, bpTK 2, bpTK 3, bpTK 4, bpTK 5 and bpTK 7, are expressed in human brain tissue and encode proteins having the amino acid sequences of SEQ ID NOS: 25-29 and 34 respectively.

Thus, the present invention includes DNA isolated from a human megakaryocytic cell line, which hybridizes to DNA encoding an amino acid sequence which is highly conserved in the catalytic domain of protein tyrosine kinases of the c-kit subgroup.

The present invention also includes the proteins encoded by the pTK genes identified as described herein, which exhibit significant sequence homology with members of the c-kit subgroup of pTKs as well as the proteins encoded by HpTK5 and the bpTKs. The present invention also includes SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK homologues or equivalents (*i.e.*, proteins which have amino acid sequences substantially similar, but not identical, to that of SAL-S1, SAL-D4, the LpTKs, HpTK5 and the bpTKs, which exhibit tyrosine kinase activity). This invention further includes peptides (SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK fragments) which retain tyrosine kinase activity, yet are less than the entire SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK sequences; and uses for the SAL-S1, SAL-D4, the LpTK, HpTK and the bpTK nucleic acid sequences and SAL-S1, SAL-D4, LpTK, HpTK and bpTK equivalents.

The present invention further includes nucleic acid sequences which hybridize with DNA or RNA encoding the proteins described herein, which exhibit significant sequence homology with the FLT/FLK, FGF receptor or NGF receptor family of protein tyrosine kinases contained within the c-kit subgroup. Such nucleic acid sequences are useful as probes to identify pTK genes in other vertebrates, particularly mammals, and in other cell types.

They can also be used as anti-sense oligonucleotides to inhibit protein tyrosine kinase activity, both *in vitro* and *in vivo*.

The SAL-S1, SAL-D4, LpTK, HpTK and bpTK tyrosine kinases of the present invention can be used as target proteins in conjunction with the development of drugs and therapeutics to modulate cell growth, differentiation and other metabolic functions. The SAL-S1, SAL-D4, LpTK, HpTK or bpTK proteins can be used as agonists or antagonists to other tyrosine kinases. The pTKs can also be instrumental in the modulation of megakaryocyte and/or platelet adhesion interactions.

In addition, the SAL-S1, SAL-D4, LpTK, HpTK and bpTK tyrosine kinases can be used in screening assays to detect cellular growth and/or differentiation factors. Using standard laboratory techniques, the ligands of the pTKs of the present invention can be identified. In particular, the invention provides chimeric pTK-immunoglobulin fusion proteins which are useful for isolating ligands to the pTKs disclosed herein. The chimeric proteins are also useful for diagnostic assays designed to detect these ligands present endogenously, within cells, as well as exogenously, in extra-cellular fluids. Assays, using the chimeric proteins, can also be designed as diagnostic aids to detect these ligands in body fluids such as blood and urine.

In another aspect, the invention provides antibodies specific for SAL-S1, SAL-D4, the LpTKs, HpTK5 and the bpTKs, which are optionally agonists for their respective pTK (where the pTK is a receptor). The invention also concerns a hybridoma cell line and an isolated nucleic acid encoding a monoclonal antibody as herein defined.

Also, the invention pertains to a method for activating a pTK as herein disclosed, comprising reacting the pTK with an agonist antibody thereto. In a different aspect, the invention concerns a method for enhancing cell growth and/or differentiation comprising administering to a human patient in need of such treatment a physiologically effective amount of an agonist antibody which activates a pTK as herein disclosed.

In a still further aspect, the invention concerns a method for detecting a pTK by contacting a source suspected of containing the pTK with a detectably labeled monoclonal antibody which reacts immunologically with the pTK, and determining whether the antibody binds to the source.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict the nucleotide sequence of SAL-S1 (SEQ ID NO: 5) and its deduced amino acid sequence (SEQ ID NO: 6).

Figures 2A and 2B depict the nucleotide sequence of SAL-D4 (SEQ ID NO: 7) and its deduced amino acid sequence (SEQ ID NO: 8).

Figure 3A depicts the nucleotide sequence of LpTK 2 (SEQ ID NO: 9) and its deduced amino acid sequence (SEQ ID NO: 10).

Figure 3B depicts the nucleotide sequence of LpTK 3 (SEQ ID NO: 11) and its deduced amino acid sequence (SEQ ID NO: 12).

Figure 3C depicts the nucleotide sequence of LpTK 4 (SEQ ID NO: 13) and its deduced amino acid sequence (SEQ ID NO: 14).

Figure 3D depicts the nucleotide sequence of LpTK 13 (SEQ ID NO: 15) and its deduced amino acid sequence (SEQ ID NO: 16).

Figures 4A-4I depict the nucleotide sequence (SEQ ID NO: 17) of SAL-S1 and its deduced amino acid sequence (SEQ ID NO: 18).

Figures 5A-5K depict the full length nucleotide sequence (SEQ ID NO: 19) of LpTK2 and its deduced amino acid sequence (SEQ ID NO: 20).

Figure 6 depicts the partial nucleotide sequence (SEQ ID NO: 21) for LpTK4.

Figures 7A-7C depict the full length nucleotide sequence (SEQ ID NO: 22) for LpTK25.

Figures 8A-8I depict the full length nucleotide sequence (SEQ ID NO: 23) and the deduced amino acid sequence of HpTK5 (SEQ ID NO: 24).

Figure 9 depicts the amino acid sequence (SEQ ID NO: 25) of bpTK1.

Figure 10 depicts the amino acid sequence (SEQ ID NO: 26) of bpTK2.

Figure 11 depicts the amino acid sequence (SEQ ID NO: 27) of bpTK3.

Figure 12 depicts the amino acid sequence (SEQ ID NO: 28) of bpTK4.

Figure 13 depicts the amino acid sequence (SEQ ID NO: 29) of bpTK5.

Figure 14 depicts the amino acid sequence (SEQ ID NO: 30) of bpTK7.

Figures 15A-15F depict the full-length nucleotide sequence of SAL-S1 (SEQ ID NO: 31) and its deduced amino acid sequence (SEQ ID NO: 32).

Figures 16A-16H depict the full-length nucleotide sequence of bpTK7 (SEQ ID NO: 33) and its deduced amino acid sequence (SEQ ID NO: 34).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Novel protein tyrosine kinase genes have been identified, their nucleic acid sequences determined, and the amino acid sequences of the encoded proteins deduced. The genes isolated as described herein are

referred to, collectively, as "protein tyrosine kinase genes" or "pTK genes".

To facilitate the isolation and identification of these novel pTKs, two sets of DNA probes were used, as described in Example 1. The first set generally consisted of two degenerative oligonucleotide sequences, pTK 1 (SEQ ID NO: 1) and pTK 2 (SEQ ID NO: 2) (Matthews, Cell 65:1143 [1991]; and Wilks, Proc. Natl. Acad. Sci. USA 86:1603 [1989]). These sequences were used as primers in a polymerase chain reaction to amplify tyrosine kinase DNA segments (Mullis, *et al.*, Cold Spring Harbor Symp. Advan. Biol. 51:263 [1986]).

The second set generally consisted of two oligonucleotide sequences, pTK 3 (SEQ ID NO: 3) and pTKKW (SEQ ID NO: 4) designed to amplify the nucleic acid sequence which encodes the highly conserved regions of the catalytic domains of the c-kit family of protein tyrosine kinases. These sequences were used as primers in the polymerase chain reaction (PCR) in a second round of DNA amplification. Using this two-step amplification procedure, DNA fragments which hybridized to these pTK primers were identified, isolated and subsequently sequenced.

In particular, fourteen pTK genes have been identified. Two pTK genes, referred to as SAL-S1 and SAL-D4, were identified in several megakaryocytic cell lines, including CMK 11-5, DAMI, UT-7 and UT-7 grown in erythropoietin, but not in the erythroid cell lines HEL, PMA stimulated HEL cells, or K562. Five pTK genes, referred to as LpTKs, were identified in lymphocytic, as well as in megakaryocytic cells. One pTK gene, referred to as HpTK5, was identified in human hepatoma cells, and six genes, referred to as bpTKs, were identified in human brain tissue.

SAL-S1 (SEQ ID NOS: 6, 18 and 32) encoded by the nucleic acid sequence of SEQ ID NOS: 5, 17 and 31 exhibits significant homology with the FLT/FLK family of pTKs. SAL-S1 has a signal peptide (*i.e.*, amino acid residues 1 to 24 of Figure 15); extracellular domain (*i.e.*, amino acid residues 25 to 775 of Figure 15); transmembrane domain (*i.e.*, amino acid residues 776 to 800 of Figure 15) and a cytoplasmic tyrosine kinase domain (*i.e.*, amino acid residues 801 to 1298 of Figure 15). SAL-D4 (SEQ ID NO: 8) encoded by SEQ ID NO: 7 is related to the CSK family of intracellular pTKs. The LpTKs, LpTK 2 (SEQ ID NOS: 10 and 20) encoded by SEQ ID NOS: 9 and 19; LpTK 3 (SEQ ID NO: 12) encoded by SEQ ID NO: 11; LpTK4 (SEQ ID NO: 14) encoded by SEQ ID NOS: 13 and 21; LpTK13 (SEQ ID NO: 16) encoded by SEQ

ID NO: 15; and LpTK25 encoded by SEQ ID NO: 22, also exhibit sequence homology with known protein tyrosine kinases.

HpTK5 (SEQ ID NO: 24) encoded by SEQ ID NO: 23 and the bpTKs 1, 2, 3, 4, 5 and 7 (SEQ ID NOS: 25-29 and 34 respectively), similarly exhibit sequence homology with known protein tyrosine kinases. BpTK7 encodes a receptor pTK with a signal peptide (*i.e.*, amino acid residues 1-19 of Figure 16); extracellular domain (*i.e.*, amino acid residues 20-547 of Figure 16); and transmembrane domain (*i.e.*, amino acid residues 548-570 of Figure 16). The remaining sequence comprises the intracellular tyrosine kinase domain.

Thus, as described above, DNA molecules which hybridize with DNA encoding amino acid sequences present in the catalytic domain of a protein tyrosine kinase of the c-kit subgroup of protein kinases have been isolated and sequenced. These isolated DNA sequences, collectively referred to as "pTK genes", (and their deduced amino acid sequences) have been shown to exhibit significant sequence homology with known members of pTK families.

Once isolated, these DNA fragments can be amplified using known standard techniques such as PCR. These amplified fragments can then be cloned into appropriate cloning vectors and their DNA sequences determined.

These DNA sequences can be excised from the cloning vectors, labeled with a radiolabeled nucleotide such as ^{32}P and used to screen appropriate cDNA libraries to obtain the full-length cDNA clone.

The pTK genes as described above have been isolated from the source in which they occur naturally, *e.g.*, megakaryocytic and lymphocytic cells. The present invention is intended to include pTK genes produced using genetic engineering techniques, such as recombinant technology, as well as pTK genes that are synthesized chemically.

The deduced amino acid sequences of the pTK genes include amino acid sequences which encode peptides exhibiting significant homology with the catalytic domain of protein tyrosine kinases of the c-kit subgroup of tyrosine kinases. These proteins, encoded by the pTK genes, can include sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence, resulting in a silent change, that is a change not detected phenotypically. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent substitution.

In addition, the protein structure can be modified by deletions, additions, inversion, insertions or substitutions of one or more amino acid residues in the sequence which do not substantially detract from the desired functional tyrosine kinase properties of the peptide.

Modified pTKs of the present invention, with tyrosine kinase activity, can be made using recombinant DNA techniques, such as excising it from a vector containing a cDNA encoding such a protein, or by synthesizing DNA encoding the desired protein mechanically and/or chemically using known techniques.

An alternate approach to producing the pTKs of the present invention is to use peptide synthesis to make a peptide or polypeptide having the amino acid sequence of such a protein, depending on the length of the pTK desired. The peptides or modified equivalents thereof, can be synthesized directly by standard solid or liquid phase chemistries for peptide synthesis.

Preferably, the pTKs of the present invention will be produced by inserting DNA encoding the proteins into an appropriate vector/host system where it will be expressed. The DNA sequences can be obtained from sources in which they occur naturally, can be chemically synthesized or can be produced using standard recombinant technology.

This invention also pertains to an expression vector comprising a pTK gene of the present invention, encoding for a protein which exhibits receptor tyrosine kinase activity.

The pTK genes of the present invention can be used for a number of diagnostic and therapeutic purposes. For example, the nucleic acid sequences of the pTK genes can be used as probes to identify other protein tyrosine kinases present in other cell types, including eukaryotic and prokaryotic cell types.

The nucleic acid sequences can also be used to design drugs that directly inhibit the kinase activity of protein tyrosine kinases, or to design peptides that bind to the catalytic domain of tyrosine kinases, thus inhibiting their activity. These sequences can also be used to design anti-sense nucleotides that can also inhibit, or destroy, tyrosine kinase activity. Such inhibition of tyrosine kinase activity would be desirable in pathological states where decreased cellular proliferation would be beneficial, such as leukemias or other malignancies.

The nucleic acid sequences can also be used to design drugs, peptides or anti-sense nucleotides as above, but with enhancing, rather than

inhibitory effects, on tyrosine kinases. Such enhanced tyrosine kinase activity would result in increasing the phosphorylation of substrates (exogenous, as well as endogenous tyrosine residues). Enhanced effects would be desirable in states where increased cellular proliferation would be beneficial, such as anemias, bleeding disorders and during surgical procedures.

The pTK genes of the present invention can also be used to obtain soluble fragments of receptor tyrosine kinases, capable of binding their respective ligands. pTK genes encoding soluble tyrosine kinase fragments can be produced using recombinant DNA techniques or synthetically. In either case, the DNA obtained encodes a soluble pTK fragment which lacks a substantial portion of the hydrophobic transmembrane region to permit solubilization of the fragment.

These soluble pTK protein fragments can be introduced exogenously to act as competitors with the endogenous, membrane bound pTK for their respective ligands, thus inhibiting tyrosine kinase activity. Alternately, a modified soluble pTK protein fragment can be introduced which binds the ligand but does not activate kinase activity.

These soluble pTK protein fragments can also be used in binding assays to detect ligands such as growth and differentiation factors. Once these ligands are identified, they may be altered or modified to inhibit or enhance kinase activity. For example, the ligands may be modified or attached to substances that are toxic to the cell, such a ricin, thus destroying the target cell. The substance may be a super-activating substance which, after binding to the pTK, may substantially increase the kinase activity, or activate other growth factors.

pTK genes of the present invention would also be useful to develop diagnostic tools for *in vitro* screening assays for ligands such as growth factors or differentiation factors that inhibit or enhance kinase activity. The proteins encoded by the pTK genes can also be used in such assays, or as immunogens to produce monoclonal or polyclonal antibodies to be used in such assays.

In one embodiment of the invention, a chimera comprising a fusion of the extracellular domain of the pTK (where the pTK is a receptor) and an immunoglobulin constant domain can be constructed which can be used to assay for ligands for the receptor and can be used for the production of antibodies against the extracellular domain of the receptor.

The expression "extracellular domain" or "ECD" when used herein refers to any polypeptide sequence that shares a ligand binding function of the extracellular domain of the naturally occurring receptor pTKs disclosed herein. Ligand binding function of the extracellular domain refers to the ability of the polypeptide to bind at least one pTK ligand. Accordingly, it is not necessary to include the entire extracellular domain since smaller segments are commonly found to be adequate for ligand binding. The truncated extracellular domain is generally soluble. The term ECD encompasses polypeptide sequences in which the hydrophobic transmembrane sequence (and, optionally, 1-20 amino acids C-terminal and/or N-terminal to the transmembrane domain) of the mature pTK has been deleted. Thus, the soluble extracellular domain-containing polypeptide can comprise the extracellular domain and the cytoplasmic domain of the pTK. Alternatively, in the preferred embodiment, the polypeptide comprises only the extracellular domain of the pTK. The extracellular and transmembrane domains of the pTK can be readily determined by the skilled practitioner by aligning the pTK of interest with known pTK amino acid sequences for which these domains have been delineated. Alternatively, the hydrophobic transmembrane domain can be readily delineated based on a hydrophobicity plot of the sequence. The extracellular domain is N-terminal to the transmembrane domain.

The term "immunoglobulin" generally refers to polypeptides comprising a light or heavy chain usually both disulfide bonded in the native "Y" configuration, although other linkage between them, including tetramers or aggregates thereof, is within the scope hereof.

Immunoglobulins (Ig) and certain variants thereof are known and many have been prepared in recombinant cell culture. For example, see U.S. Patent 4,745,055; EP 256,654; Faulkner *et al.*, Nature 298:286 [1982]; EP 120,694; EP 125,023; Morrison, J. Immun. 123:793 [1979]; Köhler *et al.*, Proc. Nat'l. Acad. Sci. USA 77:2197 [1980]; Raso *et al.*, Cancer Res. 41:2073 [1981]; Morrison *et al.*, Ann. Rev. Immunol. 2:239 [1984]; Morrison, Science 229:1202 [1985]; Morrison *et al.*, Proc. Nat'l. Acad. Sci. USA 81:6851 [1984]; EP 255,694; EP 266,663; and WO 88/03559. Reassorted immunoglobulin chains also are known. See for example U.S. patent 4,444,878; WO 88/03565; and EP 68,763 and references cited therein. The immunoglobulin moiety in the chimera of the present invention may be obtained from IgG_1, IgG_2, IgG_3, or IgG_4 subtypes, IgA, IgE, IgD or IgM, but

preferably IgG_1 or IgG_3. Most preferably, the immunoglobulin moiety is the Fc portion of IgG-γ.

The terms "chimera comprising a fusion of an extracellular domain of a pTK with an immunoglobulin constant domain sequence" or "pTK-immunoglobulin chimera" refer to a polypeptide comprising an extracellular domain coding amino acid sequence of a pTK conjugated to an immunoglobulin constant domain sequence. This definition includes chimeras in monomeric, homo- or heteromultimeric, and particularly homo- or heterodimeric, or -tetrameric forms.

A preferred embodiment is the fusion of the C-terminus of the extracellular domain of a pTK, to the N-terminus of the C-terminal portion of an antibody (in particular the Fc domain), containing the effector functions of immunoglobulin G_1. In a preferred embodiment, the entire heavy chain constant region is fused to the extracellular domain. In another preferred embodiment, a sequence beginning in the hinge region just upstream of the papain cleavage site (which defines IgG Fc chemically; residue 216, taking the first residue of heavy chain constant region to be 114 (Kabat *et al.*, Sequences of Immunological Interest, National Institutes of Health, Bethesda, MD, [1987]), or analogous sites of other immunoglobulins) is fused to the ECD of the pTK.

In a particularly preferred embodiment, the pTK extracellular domain is fused to the hinge region and C_H2 and C_H3 or C_H1, hinge, C_H2 and C_H3 domains of an IgG_1, IgG_2 or IgG_3 heavy chain. The precise site at which the fusion is made is not critical, and the optimal site can be determined by routine experimentation. A principal advantage of the chimeras is that they are secreted into the culture medium of recombinant hosts, although the degree of secretion might be different for various expression systems.

In general, the chimeras of the present invention are constructed in a fashion similar to chimeric antibodies in which a variable domain from an antibody of one species is substituted for the variable domain of another species. See, for example, EP 0 125 023; EP 173,494; Munro, Nature 312: [13 December 1984]; Neuberger *et al.*, Nature 312: [13 December 1984]; Sharon *et al.*, Nature 309: [24 May 1984]; Morrison *et al.*, Proc. Nat'l. Acad. Sci. USA 81:6851-6855 [1984]; Morrison *et al.* Science 229:1202-1207 [1985]; Boulianne *et al.*, Nature 312:643-646 [13 December 1984]; Capon *et al.*, Nature 337, 525-531 [1989]; Traunecker *et al.*, Nature 339, 68-70 [1989].

To prepare the pTK-Ig chimeric polypeptides, the DNA including a region encoding the desired pTK sequence is cleaved by a restriction enzyme at or proximal to the 3' end of the DNA encoding the immunoglobulin-like domain(s) and at a point at or near the DNA encoding the N-terminal end of the mature pTK (where use of a different leader is contemplated) or at or proximal to the N-terminal coding region for the pTK (where the native signal is employed). This DNA fragment then is readily inserted proximal to DNA encoding an immunoglobulin light or heavy chain constant region and, if necessary, the resulting construct tailored by deletional mutagenesis. Preferably, the Ig is a human immunoglobulin when the variant is intended for *in vivo* therapy for humans. DNA encoding immunoglobulin light or heavy chain constant regions is known or readily available from cDNA libraries or is synthesized. See for example, Adams *et al.*, Biochemistry 19:2711-2719 [1980]; Gough *et al.*, Biochemistry 19:2702-2710 [1980]; Dolby *et al.*, P.N.A.S. USA, 77:6027-6031 [1980]; Rice *et al.*, P.N.A.S. USA 79:7862-7865 [1982]; Falkner *et al.*, Nature 298:286-288 [1982]; and Morrison *et al.*, Ann. Rev. Immunol. 2:239-256 [1984].

The chimeric proteins disclosed herein are useful as diagnostics for isolating or screening ligands for the pTK of interest using the techniques of Lyman *et al.*, Cell 75:1157-1167 [1993], for example. Also, the chimeric proteins are useful for diagnostic purposes for studying the interaction of various ligands with the extracellular domain of the various pTKs (see, *e.g.*, Bennett *et al.*, J. Biol. Chem. 266(34):23060-23067 [1991]). The chimeric proteins are further useful for the production of antibodies against the extracellular domain of the pTK (see Examples 3 and 5 herein). The chimeric proteins also have an additional therapeutic utility insofar as they provide a soluble form of the extracellular domain of the pTK which generally has an enhanced plasma half life (compared to the extracellular domain only) and therefore can be formulated in a pharmaceutically acceptable carrier and administered to a patient. The chimeric proteins are believed to find use as therapeutic agents for removal of excess systemic or tissue-localized pTK ligand which has been administered to a patient. Removal of excess ligand is particularly desirably where the ligand may be toxic to the patient. The chimeric protein acts to bind the ligand in competition with the endogenous pTK in the patient. Similarly, it is contemplated that the chimeric protein can be administered to a patient simultaneously, or subsequent to, administration of the ligand in the form of a sustained release composition. The chimeric protein acts as a soluble

binding protein for the ligand, thereby extending the half-life of the ligand.

The term "antibody" is used herein in the broadest sense and specifically covers polyclonal antibodies, monoclonal antibodies, immunoglobulin chains or fragments thereof, which react immunologically with a pTK.

In the preferred embodiment of the invention, the antibodies are monoclonal antibodies produced using techniques which are well known in the art. For example, the hybridoma technique described originally by Kohler and Milstein, Eur. J. Immunol., 6:511 [1976], and also described by Hammerling *et al.*, In: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 [1981] can be used. The techniques of Cote *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies [Cote *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 [1985] and Boerner *et al.*, J. Immunol., 147(1):86-95 [1991]).

The term "monoclonal antibody" as used herein refers to an antibody (as hereinabove defined) obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they can be synthesized by a hybridoma culture, uncontaminated by other immunoglobulins.

"Humanized" forms of non-human (*e.g.*, murine) antibodies are immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal amino acid residues derived from a non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced

by corresponding non-human FR residues. Furthermore, a humanized antibody may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance.

The monoclonal antibodies herein include hybrid (chimeric) and recombinant antibodies produced by splicing a variable (including hypervariable) domain of an anti-pTK antibody with a constant domain (*e.g.*, "humanized" antibodies), only one of which is directed against a pTK, or a light chain with a heavy chain, or a chain from one species with a chain from another species, or fusions with heterologous proteins, regardless of species of origin or immunoglobulin class or subclass designation, so long as they are able to bind to the pTK of interest [See, *e.g.*, Cabilly, *et al.*, U.S. Patent No. 4,816,567; and Mage & Lamoyi, in Monoclonal Antibody Production Techniques and Applications, pp.79-97 (Marcel Dekker, Inc., New York [1987]).

For "chimeric" and "humanized" antibodies see, for example, U.S. Patent No. 4,816,567; WO 91/09968; EP 452,508; and WO 91/16927.

Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

In the most preferred embodiment of the invention, the antibodies are agonist antibodies. By "agonist antibody" is meant an antibody which is able to bind to, and activate, a particular pTK. For example, the agonist may bind to the extracellular domain of the pTK and thereby cause dimerization of the pTK, resulting in transphosphorylation and activation of the intracellular catalytic kinase domain. Consequently, this may result in stimulation of growth and/or differentiation of cells expressing the receptor *in vitro* and/or *in vivo*. The agonist antibodies herein are preferably against epitopes within the extracellular domain of the pTK, and preferably have the same biological characteristics as the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession No. ATCC HB 11,583. By "biological characteristics" is meant the *in vitro* and/or *in vivo* activities of the monoclonal antibody, *e.g.*, ability to activate the kinase domain of a particular pTK, ability to stimulate cell growth and/or differentiation of cells expressing the pTK, and binding characteristics of the antibody, etc. Accordingly, the antibody preferably binds to substantially the same

epitope as the anti-HpTK5 monoclonal antibody specifically disclosed herein. Most preferably, the antibody will also have substantially the same or greater antigen binding affinity of the anti-HpTK5 monoclonal antibody disclosed herein. To determine whether a monoclonal antibody has the same specificity as the anti-HpTK5 antibody specifically disclosed (*i.e.*, the antibody having the ATCC deposit No. HB 11,583), one can, for example, use a competitive ELISA binding assay.

DNA encoding the monoclonal antibodies useful in the method of the invention is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells.

The agonist antibodies disclosed herein are useful for *in vitro* diagnostic assays for activating the pTK receptor of interest. This is useful in order to study the role of the receptor in cell growth and/or differentiation.

The pTK agonist antibodies have a further therapeutic utility in a method for enhancing cell growth and/or differentiation comprising administering to a human patient in need of such treatment a physiologically effective amount of an exogenous pTK agonist antibody. Agonist antibodies to the SAL-S1 pTK may find utility in treating bleeding disorders and anemias, since this pTK was found to be expressed in megakaryocytic cells. The bpTK agonist antibodies may similarly be used to enhance differentiation and/or proliferation of brain cells in neurodegenerative diseases (such as Alzheimers disease) based on the expression of these receptors in brain tissue. Finally, HpTK5 agonist antibodies may be used to enhance proliferation of primitive hematopoietic cells in patients having undergone chemo- or radiation therapy or bone marrow transplantation.

An "exogenous" therapeutic compound is defined herein to mean a therapeutic compound that is foreign to the mammalian patient, or homologous to a compound found in the mammalian patient but produced outside the mammalian patient.

The antibodies of the present invention are also suitable for detecting a pTK by contacting a source suspected to contain the pTK with a detectably labeled monoclonal antibody, and determining whether the antibody binds to the source. There are many different labels and methods of labeling known in the art. Suitable labels include, for example, enzymes, radioisotopes, fluorescent compounds, chemi- and bioluminescent compounds, paramagnetic isotopes. The pTK may be present in biological samples, such as biological fluids or tissues. For analytical or diagnostic purposes, the antibodies of the present invention are administered in an amount sufficient to enable the detection of a site on a pTK for which the monoclonal antibody is specific. The concentration of the detectably labeled monoclonal antibody should be sufficient to give a detectable signal above background, when bound to a pTK epitope.

The pTK agonist antibodies disclosed herein may be administered to a mammal, preferably a human, in a pharmaceutically acceptable dosage form, including those that may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intramuscular, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

Such dosage forms encompass pharmaceutically acceptable carriers that are inherently nontoxic and nontherapeutic. Examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of antibody include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, liposomes, plasters, inhalation forms, nose sprays, and sublingual tablets. The antibody will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

Pharmaceutical compositions may be prepared and formulated in dosage forms by methods known in the art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition 1975.

An effective amount of the pTK agonist antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. A typical daily dosage might range from about 1 μg/kg to up to 1000 mg/kg or more, depending on the factors mentioned above. Typically, the clinician will administer the molecule until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

Depending on the type and severity of the disease, from about 0.001 mg/kg to about 1000 mg/kg, more preferably about 0.01 mg to 100 mg/kg, more preferably about 0.010 to 20 mg/kg of the agonist antibody might be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs or the desired improvement in the patient's condition is achieved. However, other dosage regimens may also be useful.

The present invention will now be illustrated by the following Examples, which are not intended to be limiting in any way. The disclosures of all literature references cited in the specification are expressly incorporated herein by reference.

EXAMPLE 1

IDENTIFICATION AND ISOLATION OF pTK GENES

To facilitate the isolation and identification of these novel pTK genes, two sets of DNA probes were generally used (see Table 1).

The first set consisted of two degenerate oligonucleotide sequences, pTK 1 (SEQ ID NO: 1) and pTK 2 (SEQ ID NO: 2). These sequences were used as polymerase chain reaction (PCR) primers, using standard PCR techniques, to amplify tyrosine kinase DNA segments.

The second set consisted of two oligonucleotide sequences, pTK 3 (SEQ ID NO: 3) and pTKKW (SEQ ID NO: 4) selected from the highly conserved regions of the catalytic domains of the c-kit subgroup of protein tyrosine kinases. These sequences were also used as polymerase chain reaction primers in a second round of DNA amplification. Using this two-step amplification procedure, DNA fragments which hybridized to these pTK primers were identified, isolated and subsequently sequenced using known laboratory techniques.

TABLE 1

First Round of Amplification

Probe name	Sequence
pTK1	5'-CGGATCCACAGNGACCT-3'
pTK2	5'-GGAATTCCAAAGGACCAGACGTC-3'

Second Round of Amplification

pTK3	(kit family specific)	5'-CGGATCCATCCACAGAGATGT-3'
pTKKW	(kit family specific)	5'-GGAATTCCTTCAGGAGCCATCCACTT-3'

EXAMPLE 2

ISOLATION AND CHARACTERIZATION OF HpTK5

A. DNA Amplification and Cloning of HpTK5

Light density human bone marrow mononuclear cells, obtained from normal volunteers using Deaconess Hospital Institutional Review Board approved protocols and with voluntary written informed consent, were separated by anti-CD34 antibody (AMAC, Westbrook, ME) and immunomagnetic beads (Dynal, Oslo, Norway). Flow cytometric analysis using FITC-conjugated anti-CD34 antibody (AMAC) confirmed ~95% CD34 positivity of isolated cells. The hepatoma cell line, Hep3B, was cultured in alpha medium (Gibco, Grand Island, NY) supplemented with penicillin (100U/mL), streptomycin (100μg/mL) and 10% fetal bovine serum (Gibco) at 37°C in a 5% CO_2 incubator. Total RNA extracted from CD34+ bone marrow mononuclear or Hep3B cells was reverse transcribed with random primers and the Moloney murine leukemia virus reverse transcriptase (RT) following the conditions of the manufacturer (Gibco-BRL) in a 20 μl reaction. PCR was performed on the RT reaction product in a 100μl reaction containing 50mM KCl, 10mM Tris·HCl (pH 8.4), 1.5mM MgCl , 20 μg/ml gelatin, 0.2mM dNTPs,

2.5 units Taq polymerase (Perkin-Elmer/Cetus) and 50pmol each of pTK-specific degenerate primers

[pTK1 5'TCGGATCCACA/CGNGAC/TC/TTGGC 3' (SEQ ID NO. 35),

pTK1B 5'TCGGATCCAC/TC/AGNGAC/TC/TTNGCNGC 3' (SEQ ID NO. 36),

pTK2 5'CTCGAATTCCA/GA/TAA/GC/GT/ACCAG/CACA/GTC 3' (SEQ ID NO. 37),

pTK2B 5'CTCGAATTCCA/GA/TAT/CC/GT/ACCAT/AACA/GTC 3'(SEQ ID NO. 38)] derived from consensus regions among known pTKs as previously reported by others (Hanks *et al.*, Science, 241:42-52 [1988]; Wilks, Proc. Nat. Acad. Sci., USA 86:1603-1607 [1989]; and Matthews *et al.*, Cell 65:1143-1152 [1991]). The PCR cycle was 1.5min at 95°C, 2min at 37°C and 3 min at 63°C repeated 35 times. The reaction product was electrophoretically separated on a 2% low-melting agarose gel, purified on an Elutip-D column (Schleicher & Schuell) digested with EcoR1 and BamH1, and subcloned into pUC19.

Recombinants were sequenced by the Sanger dideoxy method and evaluated by the FASTA nucleic acid sequence analysis program. One clone termed HpTK5 (214 bp) was radiolabelled by random priming and used to screen an oligo dT-primed lambda gt10 Hep3B cDNA library. DNA was isolated from 17 positive phage plaques and inserts were subcloned into the EcoR1 site of pBluescript (Stratagene La Jolla, CA). The largest insert, a 3969 bp cDNA, was sonicated to an average size of 800-2000 bp and cloned into the Sma1 site of M13. Overlapping clones were sequenced using the Taq Dye Primer Cycle Method (CABI) on the Catalyst 800 Molecular Biology Lab Station (ABI). Sequencing reactions were then analyzed on the ABI 373A Automated DNA Sequenator.

A single full-length 3969 bp cDNA was isolated and sequenced. (Figures 8A-8F). The full length clone, named hepatoma transmembrane kinase (HTK) or HpTK5, included an open reading frame extending from nucleotide 90 to 3050 predicted to encode a 987 amino acid protein of 108,270 Dalton. The putative initiation codon is preceded by an in-frame stop codon beginning at base 78. Preceding the open reading frame is a 5' untranslated region which is GC-rich as is characteristic for many growth factors or growth factor receptors (Kozak, J. Cell Biol. 115:887-903 [1991]).

The predicted protein sequence includes a transmembrane region (aa 538-563) which divides HpTK5 into extracellular (ECD) and intracellular domains (ICD). The ECD of 538 amino acids includes a signal peptide of 15 amino acids and a cysteine-rich box containing 20 Cys residues. In

addition, there are two fibronectin type III repeats spanning aa 321 to 425 and 435 to 526. Asn at positions 208, 340 and 431 are possible sites for N-glycosylation.

The putative intracellular domain (ICD) contains a kinase consensus region from position 613 through 881. This kinase region includes a putative ATP-binding consensus (Gly-X-Gly-X-X-Gly) in subdomain I at positions 622-627. A Lys at position 647 (subdomain II) corresponds to an invariant Lys among tyrosine kinases thought to be critical for the phosphotransfer reaction. Signature regions indicative of substrate specificity suggest that HpTK5 is a tyrosine rather than a serine/threonine kinase. These include the sequence at positions 740-745 in subdomain VI and the sequence at positions 783-790 in subdomain VIII. Tyrosine residues at positions 601, 619 and 741 are possible substrates for tyrosine kinase activity.

The predicted amino acid sequence of HpTK5 most closely resembles that of the subfamily originally defined by *EPH*. The pattern of expression of the *EPH* subfamily is suggestive of a role in differentiation and development. In particular, the emergence of neural elements corresponds with the expression of certain *EPH*-related genes. The *EPH* family receptors, Hek2 and Elk, are the most closely related pTKs to HpTK5. They share 79.3 and 76.5% identity within the ICD respectively and 45 and 42% identity within the ECD respectively.

B. Chromosome Mapping of HpTK5

Somatic cell hybrid DNAs from a panel of 25 human-hamster cell lines (Bios, New Haven, CN) were used for chromosome localization by PCR. Two sets of primers from the 3' untranslated region of HpTK5 were chosen. PCR was performed with 250 ng DNA and 50 pmol each of the 5' and 3' primers, 50 mM KCl, 1.5mM $MgCl_2$, 20 μg/ml gelatin, 0.2 mM dNTPs and 2.5 units Taq polymerase in a final volume of 100 μl. Cycles of 94°C for 30 sec, 60°C for 30 sec and 72°C for 30 sec were repeated 30 times. A portion of each sample (15 μl) was electrophoresed through a 1.5% agarose gel, transferred to a nylon membrane and hybridized to a ^{32}P-labelled full length HpTK5 cDNA probe prior to 5 hour autoradiography. Positives were scored and compared to a matrix summary of human chromosomal material present in each of the somatic cell hybrid DNAs.

The 3'-untranslated region characteristically contains few, if any, intervening sequences and has a high degree of diversity among members

of gene families making it preferred in this type of analysis. Both sets of primers gave results that were consistent with human chromosome 7 only. Human chromosome 7 also includes the genes for the EGF receptor, hepatocyte growth factor (HGF) receptor, HGF, platelet-derived growth factor (PDGF) and interleukin-6. Karyotypic abnormalities involving this chromosome are common among human leukemias, particularly in aggressive myeloid leukemias that occur following radiation, alkylating agent chemotherapy or a pre-existing myelodysplastic condition (Baer *et al.*, Curr. Opin. Oncol. 4:24-32 [1992]).

C. Northern Blotting of HpTK5

Poly-A selected RNA was electrophoresed through a 1.2% agarose, 2.2M formaldehyde gel and transferred to a nylon filter. Prepared or commercially obtained filters were hybridized in 50% formamide at 42°C to ^{32}-P labeled HpTK5, glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) or actin cDNA inserts and washed under stringent conditions (final wash: 0.1 x SSC, 0.2% SDS at 65°C). SSC is 0.15 M NaCl/ 0.015M Na_3 citrate, pH 7.6. Northern blots of human fetal or adult tissue RNA were obtained from Clontech (Palo Alto, CA) and contained 2 μg/lane of poly A selected RNA.

Northern blot analysis of human fetal tissues revealed a single transcript of ~4Kb in heart, lung, liver and kidney, with a lesser signal detectable in brain. In adult human tissue, no signal was detectable in brain, while placenta had a particularly intense signal followed by kidney, liver, lung and pancreas. Skeletal muscle and heart were of lower signal intensity.

HpTK5 expression in human tumor cell lines was also analyzed by Northern blot analysis performed as discussed above. Cell lines derived from liver, breast (MCF 7), colon (Colo 205), lung (NCI 69), melanocyte (HM-1) or cervix (HeLa) had detectable signal of appropriate size. Message was present in select cell lines of hematopoietic origin. K562 (a primitive myeloid cell with multipotential), THP-1 (a monocytoid cell), U937 (a myelomonocytic cell line), Hep3B (a human hepatocarcinoma cell line), and CMK (of megakaryocytic origin) were all positive for HpTK5 message, but lymphoid (H9, Jurkat, JH-1, Raji, Ramos) or select other myeloid cells (KG-1 or KMT2) had no detectable transcript by Northern analysis.

Differential expression of the HpTK5 transcript in fetal versus adult brain suggests that HpTK5 may share, with other *EPH* subfamily

members, a role in events related to neural development. However, unlike some members of the *EPH* subfamily which are exclusively expressed in neurons (Maisonpierre *et al.*, *supra*), HpTK5 is widely expressed in other tissues. In particular, HpTK5 is expressed in hematopoietic cells including CD34+ hematopoietic progenitor cells. The presence of the HpTK5 message in early hematopoietic cells and cell lines of myeloid lineage, but not in cell lines derived from lymphoid cells, suggests that HpTK5 may have lineage restricted expression.

EXAMPLE 3

PRODUCTION OF POLYCLONAL ANTIBODIES TO HPTK5

An HpTK5 extracellular domain (ECD)-human IgG_1 Fc fusion gene was constructed and fusion protein produced as previously described (Bennett *et al.*, J. Biol. Chem. 266:23060-23067 [1991]). Polyclonal antibodies were generated in New Zealand White rabbits against the fusion protein; 4μg in 100μL PBS was emulsified with 100μL Freund's adjuvant (complete adjuvant for the primary injection and incomplete adjuvant for all boosts). For the primary immunization and the first boost, the protein was injected directly into the popliteal lymph nodes (Sigel *et al.*, Methods Enzymol. 93:3-12 [1983]). For subsequent boosts, the protein was injected into subcutaneous and intramuscular sites. 1.3 μg protein/kg body weight was injected every 3 weeks with bleeds taken 1 and 2 weeks following each boost. HpTK5 specificity of the immunized rabbit serum was assessed by flow cytometric analysis of NIH3T3 cells transfected with full length HpTK5 or vector alone using a 1:200 dilution of pre-immune serum or anti-HpTK5-IgG Fc serum. Significant peak shifts were observed in several HpTK5 expressing clones as compared to either pre-immune serum or vector alone transfectant controls.

EXAMPLE 4

UTILITY AND AGONIST ACTIVITY OF POLYCLONAL ANTIBODIES TO HPTK5

A. FLAG-HpTK5 Fusion Construct

Overlapping oligonucleotides encoding a 12 amino acid peptide having the sequence MDYKDDDDKKLAM (SEQ ID NO: 39) which includes the 4 amino acid antibody recognition site "FLAG" (IBI, New Haven, CT) a 5'-EcoRV restriction site and a 3'-NcoI restriction site

(5'-CCGGATATCATGGACTACAAGGACGACGATGACAAGAAGCTTGCCATGGAGCTC; SEQ ID NO: 40), were ligated into the NcoI site (base 88) of HpTK5 in the EcoRV digested Bluescript (Stratagene, La Jolla, CA) vector.

B. *In vitro* Transcription and Translation

Transcription was performed on 2 pmol of linearized HpTK5 or FLAG-HpTK5 containing plasmid at 37°C for 1 h in 50 µl volume containing 10 mM dithiothreitol, 2.5 µg bovine serum albumin, 0.25 mM each dNTP, 0.5 M m7GRNA cap (New England Biolabs, Beverly, MA), 2.5 units RNasin (Promega, Madison, WI), 3 units T3 RNA polymerase (Pharmacia, Piscataway, NJ). 1 µg of DNAase (New England Biolabs, Beverly MA) was added for 15 min at 37°C prior to phenol/chloroform extraction and ethanol precipitation. Translation was performed using the Promega rabbit reticulocyte lysate kit according to the manufacturer's specifications with or without ^{35}S-methionine (350 µCi) labeling. Sample buffer containing SDS and beta-mercaptoethanol (2-ME) was added before boiling and 10% SDS-PAGE.

C. HpTK5 Expression in NIH3T3 Cells

A 4038 bp ClaI - XbaI cDNA fragment containing 32 bp of linker sequence, 37 bp of pBluescript (Stratagene La Jolla, CA) polylinker and the entire 3969 bp HpTK5 cDNA was subcloned into the expression vector pRIS (Genentech, Inc.) under the control of the Rous sarcoma virus LTR promoter. NIH3T3 cells maintained in high glucose Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FCS were co-transfected with pRIS-HpTK5 and pNeo (an SV40 based vector containing the neomycin resistance marker) by the calcium phosphate method as described by Gorman *et al.*, in DNA Prot. Engineer. Tech. 2:3-10 [1990]. Neomycin resistant colonies were selected 48 hours after transfection with Geneticin (Gibco/BRL) at 400 µg/ml. Fourteen days later individual resistant colonies were isolated, expanded and analyzed by flow cytometry for HpTK5 expression using rabbit polyclonal antiserum.

D. Immunoprecipitation

Cells (Hep3B, control NIH3T3 or HpTK5 transfected NIH3T3) or *in vitro* translated protein (HpTK5 or FLAG-HpTK5) were used for immunoprecipitation with either serum (pre-immune or anti-HpTK5-IgG Fc) or monoclonal antibody (FLAG-specific, M2, or isotype control) (IBI,

Rochester, NY). Subconfluent cells were labeled with 200μCi/ml ^{35}S-methionine for 18 hours and lysed in lysis buffer (150 mM NaCl, 50 mM Tris-HCl pH8.0, 1 mM EDTA, 0.025 Na azide, 1% NP-40, 0.1% SDS, 10% Glycerol, 0.5% Na deoxycholate, 1 mM phenylmethylsulfonyl flouride (PMSF), 10 μg/ml aprotinin, 10 μg/ml leupeptin and 50 μM Na vanadate) for 30 min on ice. The cell lysate was centrifuged (12,000 X g) for 10 min at 4°C. Cell lysate supernatant or *in vitro* translation mixture was precleared with 0.05 volume of normal rabbit serum and adsorbed with 0.05 volume of Staphylococcus aureus protein-A Sepharose CL4B. After centrifugation, preimmune or immune serum (1:100 dilution), or monoclonal antibody, was added and rocked overnight at 4°C before 100 μl of protein-A Sepharose CL4B was added and the solution rocked 4°C for additional 2 h. Immunoprecipitates were washed, suspended in SDS/PAGE loading buffer (10% glycerol, 5% 2-ME, 2.3% SDS and 62.5mM Tris-HCl pH 6.8), heated to 95°C for 5 min and analyzed by 7.5% SDS-PAGE.

E. Cell Fractionation

Cell fractionation of Hep3B cells was performed to confirm the membrane localization of HpTK5 predicted by its amino acid sequence. Hep-3B cells (1x10^7) were labeled with 200μCi/ml ^{35}S-methionine in alpha MEM medium containing 10% dialyzed FCS overnight. The cells were washed twice with cold PBS, scraped into 1ml of cold buffer (20mM Tris-HCl pH 7.5, 2mM EDTA, 5mM EGTA, 0.25M sucrose, 0.01% leupeptin, 4mM PMSF, 10mM 2-ME) and disrupted by sonication for 40 seconds. Whole homogenates were centrifuged at 12,000 X g for 15 min, the nuclear pellets isolated and the decanted supernatant centrifuged at 140,000 X g for 40 min at 4°C to pellet membranes. The resultant supernatant served as the cytosolic (C) fraction. Nuclear (N) and membrane (M) fractions were washed and dissolved in buffer containing 0.5% NP-40 prior to immunoprecipitation. The C, N or M fractions were immunoprecipitated with an anti-HpTK5 or pre-immune (control) serum, subjected to 12% SDS-PAGE and autoradiographed. HpTK5 segregated predominantly with the membrane fraction, though immunoprecipitated material was evident to a lesser extent in cytosol.

F. Protein Kinase Assay

Immunoprecipitates were washed once with kinase buffer (25mM Hepes pH7.4, 1mM DTT, 10mM MgCl, 10mM MnCl), and resuspended in 40μl of kinase

buffer containing either unlabeled ATP or 10μCi of ^{32}P-ATP (3000Ci/mM). After a 10min incubation at 30°C, the reaction was stopped by adding 40μl of 2 X sample buffer and boiling the samples for 3min prior to electrophoresis on 8.0% SDS-PAGE gel. The dried gel was covered with 4 sheets of aluminum foil to block ^{35}S-labelled protein autoradiography and the gel was placed under film for 5 hours to overnight.

G. Western Blotting and Phosphotyrosine Assay

Proteins were electrophoretically transferred to a 0.2 μm nitrocellulose (Bio-Rad) or a 0.45μm polyvinylidene diflouride (Millipore) membrane in a buffer containing 25 mM Tris-HCl (pH 7.5), 192 mM glycine and 20% methanol at 100 mA for 2 h. Filters were washed in TBS (10 mM Tris-HCl pH 8.0, 150 mM NaCl) blocked by incubating in TBST (TBS with 0.05% Tween-20) plus 5% BSA overnight. Filters were washed four times for 5 min each in TBST and incubated for 2 h with 4G10 anti-phosphotyrosine antibody from UBI (1:1000 dilution in TBST). Filters were washed four times for 5 min each in TBST and incubated for 1 h with the alkaline phosphatase labelled anti-mouse secondary antibody (Promega) at a 1:7500 dilution in TBST. After washing four times, the blot was developed for 30-60 min in AP buffer (100mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$) plus BCIP, NBT substrates.

H. Antibody Induced Phosphorylation Assay

Rabbit antisera to HpTK5-IgG Fc were tested for their ability to induce HpTK5 phosphorylation in HpTK5 transfected NIH3T3 cells. Cells were plated at a density of 5 x 10^5 cells/well in a 6-well plate and, after 24 hours, were serum starved for 1 hour prior to adding pre-immune or immune serum at a 1:50 dilution for 30 minutes. Cells were then washed in PBS and lysed in either 2X sample buffer or NP-40 lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. HpTK5 expressing cells were exposed to antisera and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of HpTK5 was observed following exposure to polyclonal antiserum showing an agonist-like effect of antibody binding. Interaction of HpTK5 with an antibody directed against its ECD induces phosphorylation. This provides

further support that HpTK5 may serve as a receptor for a ligand that triggers kinase activation. Details of the signaling pathway of HpTK5 may be further explored using antisera as a surrogate ligand.

I. Conclusions

An HpTK5 ECD-IgG Fc fusion protein was expressed, purified and used to generate rabbit anti-serum which immunoprecipitated a 120kD protein from Hep3B cells. The specificity of the antiserum was confirmed by immunoprecipitation of *in vitro* translated HpTK5 RNA and HpTK5 transfected NIH3T3 cells. To determine the functional capacity of HpTK5, *in vitro* translated HpTK5 was immunoprecipitated, exposed to kinase conditions and immunoblotted using a phosphotyrosine specific monoclonal antibody. The data obtained indicated that HpTK5 is phosphorylated on tyrosine. However, the presence of other bands consistently appearing in the ^{32}P-labelled immunoprecipitation suggested that HpTK5 protein was only partially purified and therefore, it could not be concluded that HpTK5 was enzymatically active. To overcome this problem, a fusion construct was generated in which an 8 amino acid epitope (FLAG) was added to the N-terminus of HpTK5. The FLAG-HpTK5 fusion was *in vitro* translated and immunoprecipitated with a FLAG-specific monoclonal antibody resulting in a single protein of appropriate size (~120kD). When subjected to kinase conditions in the presence of ^{32}P-ATP, the HpTK5-FLAG fusion protein was labelled on tyrosine confirming tyrosine autophosphorylation and thereby, the kinase function of HpTK5.

EXAMPLE 5

PRODUCTION OF MONOCLONAL ANTIBODIES TO HPTK5

Anti-HpTK5 monoclonal antibodies were produced by hyperimmunizing BALB/c mice intraperitoneally with the HpTK5 extracellular domain (ECD)-human IgG_1 Fc fusion protein (produced using the techniques disclosed above) in RIBI adjuvant (RIBI ImmunoChem Research, Hamilton, MT) and fusing splenocytes with the mouse myeloma cell line X63-Ag8.653 (Kearney *et al.*, J. Immunol. 123:1548-1550 [1979]). The antibodies were purified from ascites fluid using protein A-Sepharose (Repligen Corp., Cambridge, MA) and established affinity chromatography methods (Goding, J.W., J. Immunol. Methods 20:241-253 [1978]).

Monoclonal antibodies were screened for their ability to bind the HpTK5 antigen. Starting on day 15 post fusion, culture supernatants were

harvested from the fusion plates and assayed for their ability to specifically "capture" HpTK5-IgG. In this ELISA assay, goat anti-mouse IgG was coated onto 96 well microtiter plates. The culture supernatants (100μl) were added to the wells and the mouse IgG present was bound by the goat anti-mouse IgG antibodies. The plates were washed and either HpTK5-IgG or CD4-IgG (100μl at 6nM) was added. The "captured" immunoadhesin was detected using a goat anti-hu (Fc specific) horseradish peroxidase conjugate and orthophenylene diamine substrate. Quantitation of substrate catalysis was determined by optical density at 490nm.

Agonist antibodies were then screened for using the techniques disclosed in Example 6 below. Two agonist monoclonal antibodies were identified, one of which has been deposited with the ATCC.

EXAMPLE 6

AGONIST ACTIVITY OF MONOCLONAL ANTIBODIES TO HPTK5

The monoclonal antibodies produced using the techniques disclosed in Example 5 were tested for their ability to induce HpTK5 phosphorylation in HpTK5 transfected NIH3T3 cells. Cells were plated at a density of 5 x 10^5 cells/well in a 6-well plate and, after 24 hours, were serum starved for 1 hour prior to adding pre-immune serum or anti-HpTK5 monoclonal antibody (undiluted conditioned hybridoma media was used) for 30 minutes. Cells were then washed in PBS and lysed in either 2X sample buffer or NP-40 lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. HpTK5 expressing cells were exposed to the monoclonal antibody and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of HpTK5 was observed following exposure to monoclonal antibodies showing an agonist-like effect of antibody binding. Accordingly, interaction of HpTK5 with a monoclonal antibody directed against its ECD is able to induce phosphorylation of the kinase domain thereof.

EXAMPLE 7

PRODUCTION OF POLYCLONAL ANTIBODIES TO SAL-S1

A SAL-S1 extracellular domain (ECD)-human IgG_1 Fc fusion gene was constructed and fusion protein produced as previously described in

Bennett *et al.*, J. Biol. Chem. 266:23060-23067 [1991]. Briefly, PCR primers otk 1.41.1 (SEQ ID NO: 43) and otk 1.41.2 (SEQ ID NO: 44) were employed in the PCR technique using plasmid pRK5.tk1-1.1 (SEQ ID NO: 45) containing SAL-S1 nucleic acid as a template to create a DNA fragment which, when digested with SalI/BstEII, generated an 155bp SalI/BstEII fragment. This 155bp fragment was combined with a 6839bp SalI/HindIII fragment isolated from pRK5.tk1-1.1 and a 719 bp BstEII/HindIII fragment isolated from pBSSK-CH2-CH3 (Bennett *et al.*, *supra*). These fragments were ligated together to create a plasmid pRK5.tk1.ig1.1 (7713bp in size) which, when transfected into 293 cells, was used to produce a SAL-S1 extracellular domain (ECD)-human IgG Fc fusion protein. Fusion protein was prepared and purified as described in Bennett *et al.*, *supra*. Polyclonal antibodies were generated in female New Zealand White rabbits against the fusion protein. Briefly, 12.5μg of fusion protein in 0.625ml PBS was emulsified with 0.625ml Freund's adjuvant (complete adjuvant for the primary injection and incomplete adjuvant for all boosts). The primary injection and all boosts were intramuscular at two sites and subcutaneous at multiple sites. Boosts were carried out at 3 week intervals with bleeds taken 1 and 2 weeks following each boost. SAL-S1 specificity of the immunized rabbit serum was assessed by flow cytometric analysis of 293 (ATCC CRL 1593) and COS7 (ATCC CRL 1651) cells transfected with full length SAL-S1 or vector alone (see below) using a 1:200 dilution of pre-immune serum or anti-SAL-S1-IgG Fc serum. Significant peak shifts were observed in several SAL-S1 expressing clones as compared to either pre-immune serum or vector alone transfectant controls.

EXAMPLE 8

UTILITY AND AGONIST ACTIVITY OF SAL-S1 POLYCLONAL ANTIBODIES

A. Immunoprecipitation

Control 293 and COS7 cells as well as SAL-S1 transfected 293 and COS7 cells were used for immunoprecipitation with either pre-immune serum or anti-SAL-S1-IgG Fc polyclonal antibody. COS7 and 293 cells were transfected using a $CaPO_4$ procedure as described by Gorman, C. DNA Cloning, Glover D. Ed., IRL Press, Oxford, vol2: 143-190 (1985). For transient expression, 293 cells were transfected as described by Gearing *et al.* EMBO 8: 3667-3676 (1989). Subconfluent cells were labeled with 200μCi/ml ^{35}S- methionine for 18 hours and lysed in lysis buffer (150 mM

NaCl, 50mM HEPES, pH 7.5, 1 mM EGTA, 0.025 Na azide, 1% Triton-X 100, 1.5mM $MgCl_2$, 10% Glycerol, 1 mM phenylmethylsulfonyl flouride [PMSF], 10 μg/ml aprotinin, 10 μg/ml leupeptin and 50 μM Na vanadate) for 10 min on ice. The cell lysate was centrifuged (12,000 X g) for 10 min at 4°C. After centrifugation, preimmune or polyclonal antibody was added to the supernatant and rocked for 4 hrs at 4°C before 100 μl of protein-A Sepharose CL4B was added and the solution rocked 4°C for additional 2 h. Immunoprecipitates were washed, suspended in SDS/PAGE loading buffer (10% glycerol, 5% 2-ME, 2.3% SDS and 62.5mM Tris-HCl pH 6.8), heated to 95°C for 5 min and analyzed by 7.5% SDS-PAGE.

B. Western Blotting and Phosphotyrosine Assay

Proteins were electrophoretically transferred to a 0.2 μm nitrocellulose (Bio-Rad) or a 0.45μm polyvinylidene diflouride (Millipore) membrane in a buffer containing 25 mM Tris-HCl (pH 7.5), 192 mM glycine and 20% methanol at 100 mA for 2 h. Filters were washed in TBS (10 mM Tris-HCl pH 8.0, 150 mM NaCl) blocked by incubating in TBST (TBS with 0.05% Tween-20) plus 5% BSA overnight. Filters were washed four times for 5 min each in TBST and incubated for 2 h with 4G10 anti-phosphotyrosine antibody from UBI (1:1000 dilution in TBST). Filters were washed four times for 5 min each in TBST and incubated for 1 h with the alkaline phosphatase labelled anti-mouse secondary antibody (Promega) at a 1:5000 dilution in TBST. After washing four times, the blot was developed for 30-60 min in AP buffer (100mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$) plus BCIP, NBT substrates.

C. Antibody Induced Phosphorylation Assay

Rabbit antisera to SAL-S1-IgG Fc were tested for their ability to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells. Cells were plated at a density of 5 x 10^5 cells/well in a 6-well plate and, after 24 hours, were serum starved for 12 hours prior to adding pre-immune or immune serum at a 1:5 dilution for 30 minutes. Cells were then washed in PBS and lysed in either sample buffer or Triton-X lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 8% or 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. SAL-S1 expressing cells were exposed to antisera and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted

with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of SAL-S1 was observed following exposure to polyclonal antiserum showing an agonist-like effect of antibody binding. Interaction of SAL-S1 with an antibody directed against its ECD induces phosphorylation.

EXAMPLE 9

PRODUCTION OF MONOCLONAL ANTIBODIES TO SAL-S1

Anti-SAL-S1 monoclonal antibodies were produced by hyperimmunizing BALB/c mice in the foot pad with the SAL-S1 extracellular domain-human IgG_1 Fc fusion protein in RIBI adjuvant (RIBI Immunochem Research, Hamilton, MT) and fusing lymphocyte from lymph nodes with the mouse myeloma cell line X63-Ag8U1.

Starting on day 10 post fusion, cultured supernatants were harvest from the fusion plates and assayed for their ability to bind to SAL-S1. In this ELISA assay, SAL-S1 IgG_1 was coated onto 96 microtiter plates. The cultured supernatants (100μl) were added to the wells and the mouse antibodies present were bound to Sal-S1 IgG_1. The plates were washed and mouse IgG was detected using a goat anti-mouse IgG (Fc specific with no cross reactivity against human IgG Fc) horseradish peroxidase conjugate and orthophenylene diamine substrate. Quantitation of substrate catalysis was determined by optical density at 490 nm.

Cultured supernatants which were positive from ELISA were then tested for their ability to specifically bind to 293 transfected with SAL-S1 receptor and analyzed by flow cytometry. Agonist antibodies were then screened for using the techniques disclosed in Example 10 below. Six agonist monoclonal antibodies were identified.

EXAMPLE 10

AGONIST ACTIVITY OF MONOCLONAL ANTIBODIES TO SAL-S1

The monoclonal antibodies were tested for their ability to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells. Cells were harvested from tissue culture dish by assay buffer and washed 2x with the same buffer. $1x10^5$ cells were added to a 96 U-bottom plate which was centrifuged and assay buffer was removed. 150 μl of cultured supernatants was added to each well followed by incubation at 37°C for 30 minutes, the plate was centrifuged and cultured supernatants were removed. 100 μl of Fixing solution was added, the cells were fixed for 30 minutes at -20°C, cells were washed with buffer 2x and stained with anti-phosphotyrosine

conjugate with FITC for 60 minutes at 4°C. Cells were analyzed by flow cytometry (FACScan Becton Dickinson, milplitas, CA). The six anti-SAL-S1 monoclonal antibodies were able to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells.

Deposit of Materials

The following culture has been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD, USA (ATCC):

Hybridoma	ATCC No.	Deposit Date
Anti-HpTK5	HB 11,583	March 15, 1994

This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture for 30 years from the date of deposit. The organism will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if the culture on deposit should die or be lost or destroyed when cultivated under suitable conditions, it will be promptly replaced on notification with a viable specimen of the same culture. Availability of the deposited strain is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the culture deposited, since the deposited embodiment is intended as a single illustration of one aspect of the invention and any culture that are functionally equivalent

are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustration that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Genentech, Inc.
Bennett, Brian D.
Goeddel, David
Lee, James M.
Matthews, William
Tsai, Siao Ping
Wood, William I.

(ii) TITLE OF INVENTION: PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

(iii) NUMBER OF SEQUENCES: 45

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genentech, Inc.
(B) STREET: 460 Point San Bruno Blvd
(C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 5.25 inch, 360 Kb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: patin (Genentech)

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/222616
(B) FILING DATE: 04-APR-1994

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Wendy M. Lee
(B) REGISTRATION NUMBER: 00,000
(C) REFERENCE/DOCKET NUMBER: 821P3PCT

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 415/225-1994
(B) TELEFAX: 415/952-9881
(C) TELEX: 910/371-7168

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGGATCCACA GNGACCT 17

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GGAATTCCAA AGGACCAGAC GTC 23

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGGATCCATC CACAGAGATG T 21

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGAATTCCTT CAGGAGCCAT CCACTT 26

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 bases
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCTGTG CATCAGTGAC TTAGGGCTAG GAACATTCTG CTGTCGGAAA 50

GCGACGTGGT GAAGATCTGT GACTTTGGCC TTGCCCGGGA CATCTACAAA 100

GACCCCAGCT ACGTCCGCAA GCATGCCCGG CTGCCCCTGA AGTGGATGGC 150

GCCAGAATTC 160

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Asp Pro Val His Gln Xaa Leu Arg Ala Arg Asn Ile Leu Leu Ser
1 5 10 15

Glu Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp
20 25 30

Ile Tyr Lys Asp Pro Ser Tyr Val Arg Lys His Ala Arg Leu Pro
35 40 45

Leu Lys Trp Met Ala Pro Glu Phe
50 53

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 147 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGATCCATTC ACAGAGACCT AGCAGCACGC AACATCCTGG TCTCAGAGGA 50

CCTGGTAACC AAGGTCAGCG ACTTTGGCCT GGCCAAAGCC GAGCGGAAGG 100

GGCTAGACTC AAGCCGGCTG CCCGTCAAAT GGATGGCTCC CGAATTC 147

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Gly Ser Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ser
1 5 10 15

Glu Asp Leu Val Thr Lys Val Ser Asp Phe Gly Leu Ala Lys Ala
20 25 30

Glu Arg Lys Gly Leu Asp Ser Ser Arg Leu Pro Val Lys Trp Met
35 40 45

Ala Pro Glu Phe
49

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 149 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GTTGGAATTC CTTCCGGCGC CATCCATTTC ACCGGCAGCT TTATTTCGTG 50

TCTAGATTCA TAGATGTCTT CATTATCTAC CTTAAAAACT CTGGCAAGTC 100

CAAAATCTGC TACTTTGTAG ATATTATGTT CACCAACGAG GACATTCCT 149

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Val Gly Ile Pro Ser Gly Ala Ile His Phe Thr Gly Ser Phe Ile
1 5 10 15

Ser Cys Leu Asp Ser Met Ser Ser Leu Ser Thr Leu Lys Thr Leu
20 25 30

Ala Ser Pro Lys Ser Ala Thr Leu Ile Leu Cys Ser Pro Thr Arg
35 40 45

Thr Phe
47

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GTGCACAGGG ATCTCGCGGC TCGGAACATC CTCGTCGGGG AAAACACCCT 50

CTCGAAAGTT GGGGACTTCG GGTTAGCCAG GCTTATCAAG GAGGACGTCT 100

ACCTCTCCCA TGACCACAAT ATCCCCTACA AATGGATGGC CCCTGAGGGA 150

A 151

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Gly Glu Asn
1 5 10 15

Thr Leu Ser Lys Val Gly Asp Phe Gly Leu Ala Arg Leu Ile Lys
20 25 30

Glu Asp Val Tyr Leu Ser His Asp His Asn Ile Pro Tyr Lys Trp
35 40 45

Met Ala Pro Glu Gly
50

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 137 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTTCACCGAG ATCTCAAGTC CAACAACATT TTGCTGCTGC AGCCCATTGA 50

GAGTGACGAC ATGGAGCACA AGACCCTGAA GATCACCGAC TTTGGCCTGG 100

CCCGAGAGTG GCACAAAACC ACACAAATGA GTGCCGC 137

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Val His Arg Asp Leu Lys Ser Asn Asn Ile Leu Leu Leu Gln Pro
1 5 10 15

Ile Glu Ser Asp Asp Met Glu His Lys Thr Leu Lys Ile Thr Asp
20 25 30

Phe Gly Leu Ala Arg Glu Trp His Lys Thr Thr Gln Met Ser Ala
35 40 45

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 211 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCAATCGTG ACCTCGCCGC CCGAAATGTG TTGCTAGTTA CCCAACATTA 50

CGCCAAGATC AGTGATTTCG GACTTTCCAA AGCACTGCGT GCTGATGAAA 100

ACTACTACAA GGCCCAGACC CATGGAAAGT GGCCTGTCAA GTGGTACGCT 150

CCGGAATGCA TCAACTACTA CAAGTTCTCC AGCAAAAGCG ATGTCTGGTC 200

CTTTGGAATT C 211

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 70 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Val Asn Arg Asp Leu Ala Ala Arg Asn Val Leu Leu Val Thr Gln
1 5 10 15

His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Arg
20 25 30

Ala Asp Glu Asn Tyr Tyr Lys Ala Gln Thr His Gly Lys Trp Pro
35 40 45

Val Lys Trp Tyr Ala Pro Glu Cys Ile Asn Tyr Tyr Lys Phe Ser
50 55 60

Ser Lys Ser Asp Val Trp Ser Phe Gly Ile
65 70

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6827 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA 700

TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACTTGGCT TCGTTAGAAC GCGGCTACAA TTAATACATA 800

ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA GAATAACATC 850

CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900

CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT 950

CGAGATCCAT TGTGCTGGCG CGGATTCTTT ATCACTGATA AGTTGGTGGA 1000

CATATTATGT TTATCAGTGA TAAAGTGTCA AGCATGACAA AGTTGCAGCC 1050

GAATACAGTG ATCCGTGCCG CCCTAGACCT GTTGAACGAG GTCGGCGTAG 1100

ACGGTCTGAC GACACGCAAA CTGGCGGAAC GGTTGGGGGT TCAGCAGCCG 1150

GCGCTTTACT GGCACTTCAG GAACAAGCGG GCGCTGCTCG ACGCACTGGC 1200

CGAAGCCATG CTGGCGGAGA ATCATAGCAC TTCGGTGCCG AGAGCCGACG 1250

ACGACTGGCG CTCATTTCTG ACTGGGAATG CCCGCAGCTT CAGGCAGGCG 1300

CTGCTCGCCT ACCGCCAGCA CAATGGATCT CGAGGGATCT TCCATACCTA 1350

CCAGTTCTGC GCCTGCAGGT CGCGGCCGCA CTACTCTTTG ATGTATTACT 1400

CATATTACCA AGGAATAACT GGCGGGCACA GGGTCAGGTG CTGAAGGGAC 1450

ATTGTGAGAA GTGACCTAGA AGGCAAGAGG TGAGCCCTCT GTCACGCTGG 1500

CATAAGGGCC GCTTGAGGGC TCTTTGGTCA AGCAGTAACG CCAGTGTCTG 1550

GGAAGGCACC TGTTACTCAG CAGACCATGA AAGGGCGTCT CCCTTTCCTT 1600

GGAGCAGTCA GGGAACACTC TGCTCCACCA GCTTCTTGTG GGAGCCTGGA 1650

TATTATCCAG GCCTGCCCGC AGTCATCCGG AGGCCTAACC CCTCCCTGTG 1700

GTGCTTCAGT GGTCACACTC CTTGTCCACT TTCATGCTCC TCTTGGCCTC 1750

CTGGTTCCTC TTGGAAGTTT GTAGTAGATA GCAGAAGAAA TAGCGAAAGT 1800

CTTAAAGTCT TTGATCTTTC TTATAAGTGC AGAGAAGAAA TGCTGACGTA 1850

TGCTGCCTTC TCTCTCTCTG CTTCAGCTAC CTGAAGCCGC TTTCTTGTCT 1900

ATACCTGCTC TCTATCTGCT CACACTCCTC CGAGGCCAGC ACCATCCCAC 1950

TGTCTGTCTG GTTGTCCACA GAGCCTTTGT AGGTCGTTGG GGTCATGGGG 2000

AATTCCTCAA ATGTCTTCAT CCTGGAGGAA CCACGGGTCT CAGCCCCTCT 2050

GGCCAGGCAC CCGGGAAAGG ACACCCAGTT GTAATACCTG GCGGCCAGGC 2100

TGTGGCGCTG CAGGCTTGGC GGGCTGTCCT CAGCGTCAGC CTGGGCGATG 2150

TGTAGGGCCA TGGTGGACAC CTGCGAGAAG CTGCCCTCTT CTGAGCTCTG 2200

AGAGCTGCGC GGGGCCATGC AGACCTCCTC TTCCTCTTGC AGGCCCCTGC 2250

CCTGGAGCAG GTCCCCCAGG ATCTCCACCA GCTCCGAGAA TGCAGGTCTC 2300

GCCTTGGGGT CTCCGGACCA GCAGTTCAGC ATGATGCGGC GTATGGCGGG 2350

AGTGGCCAGC TCCGGGGCCC TCATCCTTGT GCCGTCTCTC AGCCGCTGGC 2400

AGAACTCCTC ATTGATCTGC ACCCCAGGGT ACGGGGAGGC CCCCAGAGAG 2450

AAGATCTCCC AGAGAAGCAC CCCAAAGGAC CACACGTCAC TCTGCGTGGT 2500

GTACACCTTG TCGAAGATGC TTTCAGGGGC CATCCACTTC AGGGGCAGCC 2550

GGGCACTGCC CTTGCGGACG TAGTCGGGGT CTTTGTAGAT GTCCCGGGCA 2600

AGGCCAAAGT CACAGATCTT CACCACGTCG CTTTCCGACA GCAGAATGTT 2650

CCGAGCAGCC AGGTCTCTGT GGATGCACTT TCGGGAAGCC AGGAACTCCA 2700

TCCCTCTGGC CACCTGGAAG CTGTAGCAGA CAAGATCTTC CATGGTCAGC 2750

GGGCTCAGCC ACAGGTCCTC AGCTTCTTGG TCTGGAGAAG CCCGCCTCGC 2800

TCCGCCCTCG GTCTTCGAGA ACCGCGCGAA GAGGACCCTG TCGCTGCTCC 2850

CCGGCCGCCT CCGATCCAGC CTGGCGAGCT CCACCATGGC GCGGAAGCGT 2900

CCGCGCTGCT CGGGAGACTT CTCCTGCGGA TGCACGAAGC TGGCTCGAGG 2950

GCGCCCAGTC GTCCGCCGCA GAGGCGCCTC CATTCCCCCG CCGCCCGCGG 3000

CGCCCCGCAG GCCGCCCGCT CACCGNGCAG GGGCTGCGGC CGCGACTCTA 3050

GAGTCGACCT GCAGAAGCTT GGCCGCCATG GCCCAACTTG TTTATTGCAG 3100

CTTATAATGG TTACAAATAA AGCAATAGCA TCACAAATTT CACAAATAAA 3150

GCATTTTTTT CACTGCATTC TAGTTGTGGT TTGTCCAAAC TCATCAATGT 3200

ATCTTATCAT GTCTGGATCG ATCGGGAATT AATTCGGCGC AGCACCATGG 3250

CCTGAAATAA CCTCTGAAAG AGGAACTTGG TTAGGTACCT TCTGAGGCGG 3300

AAAGAACCAG CTGTGGAATG TGTGTCAGTT AGGGTGTGGA AAGTCCCCAG 3350

GCTCCCCAGC AGGCAGAAGT ATGCAAAGCA TGCATCTCAA TTAGTCAGCA 3400

ACCAGGTGTG GAAAGTCCCC AGGCTCCCCA GCAGGCAGAA GTATGCAAAG 3450

CATGCATCTC AATTAGTCAG CAACCATAGT CCCGCCCCTA ACTCCGCCCA 3500

TCCCGCCCCT AACTCCGCCC AGTTCCGCCC ATTCTCCGCC CCATGGCTGA 3550

CTAATTTTTT TTATTTATGC AGAGGCCGAG GCCGCCTCGG CCTCTGAGCT 3600

ATTCCAGAAG TAGTGAGGAG GCTTTTTTGG AGGCCTAGGC TTTTGCAAAA 3650

AGCTGTTAAC AGCTTGGCAC TGGCCGTCGT TTTACAACGT CGTGACTGGG 3700

AAAACCCTGG CGTTACCCAA CTTAATCGCC TTGCAGCACA TCCCCCCTTC 3750

GCCAGCTGGC GTAATAGCGA AGAGGCCCGC ACCGATCGCC CTTCCCAACA 3800

GTTGCGTAGC CTGAATGGCG AATGGCGCCT GATGCGGTAT TTTCTCCTTA 3850

CGCATCTGTG CGGTATTTCA CACCGCATAC GTCAAAGCAA CCATAGTACG 3900

CGCCCTGTAG CGGCGCATTA AGCGCGGCGG GTGTGGTGGT TACGCGCAGC 3950

GTGACCGCTA CACTTGCCAG CGCCCTAGCG CCCGCTCCTT TCGCTTTCTT 4000

CCCTTCCTTT CTCGCCACGT TCGCCGGCTT TCCCCGTCAA GCTCTAAATC 4050

GGGGGCTCCC TTTAGGGTTC CGATTTAGTG CTTTACGGCA CCTCGACCCC 4100

AAAAAACTTG ATTTGGGTGA TGGTTCACGT AGTGGGCCAT CGCCCTGATA 4150

GACGGTTTTT CGCCCTTTGA CGTTGGAGTC CACGTTCTTT AATAGTGGAC 4200

TCTTGTTCCA AACTGGAACA ACACTCAACC CTATCTCGGG CTATTCTTTT 4250

GATTTATAAG GGATTTTGCC GATTTCGGCC TATTGGTTAA AAAATGAGCT 4300

GATTTAACAA AAATTTAACG CGAATTTTAA CAAAATATTA ACGTTTACAA 4350

TTTTATGGTG CACTCTCAGT ACAATCTGCT CTGATGCCGC ATAGTTAAGC 4400

CAACTCCGCT ATCGCTACGT GACTGGGTCA TGGCTGCGCC CCGACACCCG 4450

CCAACACCCG CTGACGCGCC CTGACGGGCT TGTCTGCTCC CGGCATCCGC 4500

TTACAGACAA GCTGTGACCG TCTCCGGGAG CTGCATGTGT CAGAGGTTTT 4550

CACCGTCATC ACCGAAACGC GCGAGGCAGT ATTCTTGAAG ACGAAAGGGC 4600

CTCGTGATAC GCCTATTTTT ATAGGTTAAT GTCATGATAA TAATGGTTTC 4650

TTAGACGTCA GGTGGCACTT TTCGGGGAAA TGTGCGCGGA ACCCCTATTT 4700

GTTTATTTTT CTAAATACAT TCAAATATGT ATCCGCTCAT GAGACAATAA 4750

CCCTGATAAA TCTTCAATAA TATTGAAAAA GGAAGAGTAT GAGTATTCAA 4800

ACATTTCCGT GTCGCCCTTA TTCCCTTTTT GGCGGCATTT TGCCTTCCTG 4850

TTTTTGCTCA CCCAGAAACG CTGGTGAAAG TAAAAGATGC TGAAGATCAG 4900

TTGGGTGCAC GAGTGGGTTA CATCGAACTG GATCTCAACA GCGGTAAGAT 4950

CCTTGAGAGT TTTCGCCCCG AAGAACGTTT TCCAATGATG AGCACTTTTA 5000

AAGTTCTGCT ATGTGGCGCG GTATTATCCC GTGATGACGC CGGGCAAGAG 5050

CAACTCGGTC GCCGCATACA CTATTCTCAG AATGACTTGG TTGAGTACTC 5100

ACCAGTCACA GAAAAGCATC TTACGGATGG CATGACAGTA AGAGAATTAT 5150

GCAGTGCTGC CATAACCATG AGTGATAACA CTGCGGCCAA CTTACTTCTG 5200

ACAACGATCG GAGGACCGAA GGAGCTAACC GCTTTTTTGC ACAACATGGG 5250

GGATCATGTA ACTCGCCTTG ATCGTTGGGA ACCGGAGCTG AATGAAGCCA 5300

TACCAAACGA CGAGCGTGAC ACCACGATGC CAGCAGCAAT GGCAACAACG 5350

TTGCGCAAAC TATTAACTGG CGAACTACTT ACTCTAGCTT CCCGGCAACA 5400

ATTAATAGAC TGGATGGAGG CGGATAAAGT TGCAGGACCA CTTCTGCGCT 5450

CGGCCCTTCC GGCTGGCTGG TTTATTGCTG ATAAATCTGG AGCCGGTGAG 5500

CGTGGGTCTC GCGGTATCAT TGCAGCACTG GGGCCAGATG GTAAGCCCTC 5550

CCGTATCGTA GTTATCTACA CGACGGGGAG TCAGGCAACT ATGGATGAAC 5600

GAAATAGACA GATCGCTGAG ATAGGTGCCT CACTGATTAA GCATTGGTAA 5650

CTGTCAGACC AAGTTTACTC ATATATACTT TAGATTGATT TAAAACTTCA 5700

TTTTTAATTT AAAAGGATCT AGGTGAAGAT CCTTTTTGAT AATCTCATGA 5750

CCAAAATCCC TTAACGTGAG TTTTCGTTCC ACTGAGCGTC AGACCCCGTA 5800

GAAAAGATCA AAGGATCTTC TTGAGATCCT TTTTTTCTGC GCGTAATCTG 5850

CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTTTGCCGG 5900

ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG 5950

CAGATACCAA ATACTGTCCT TCTAGTGTAG CCGTAGTTAG GCCACCACTT 6000

CAAGAACTCT GTAGCACCGC CTACATACCT CGCTCTGCTA ATCCTGTTAC 6050

CAGTGGCTGC TGCCAGTGGC GATAAGTCGT GTCTTACCGG GTTGGACTCA 6100

AGACGATAGT TACCGGATAA GGCGCAGCGG TCGGGCTGAA CCGGGGGTTC 6150

GTGCACACAG CCCAGCTTGG AGCGAACGAC CTACACCGAA CTGAGATACC 6200

TACAGCGTGA GCATTGAGAA AGCGCCACGC TTCCCGAAGG GAGAAAGGCG 6250

GACAGGTATC CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGA 6300

GCTTCCAGGG GGAAACGCCT GGTATCTTTA TAGTCCTGTC GGGTTTCGCC 6350

ACCTCTGACT TGAGCGTCGA TTTTTGTGAT GCTCGTCAGG GGGGCGGAGC 6400

CTATGGAAAA ACGCCAGCAA CGCGGCCTTT TTACGGTTCC TGGCCTTTTG 6450

CTGGCCTTTT GCTCACATGT TCTTTCCTGC GTTATCCCCT GATTCTGTGG 6500

ATAACCGTAT TACCGCCTTT GAGTGAGCTG ATACCGCTCG CCGCAGCCGA 6550

ACGACCGAGC GCAGCGAGTC AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT 6600

ACGCAAACCG CCTCTCCCCG CGCGTTGGCC GATTCATTAA TCCAGCTGGC 6650

ACGACAGGTT TCCCGACTGG AAAGCGGGCA GTGAGCGCAA CGCAATTAAT 6700

GTGAGTTACC TCACTCATTA GGCACCCCAG GCTTTACACT TTATGCTTCC 6750

GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA 6800

ACAGCTATGA CCATGATTAC GAATTAA 6827

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 348 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe Arg Ala Met Val Glu
1 5 10 15

Leu Ala Arg Leu Asp Arg Arg Arg Pro Gly Ser Ser Asp Arg Val
20 25 30

Leu Phe Ala Arg Phe Ser Lys Thr Glu Gly Gly Ala Arg Arg Ala
35 40 45

Ser Pro Asp Gln Glu Ala Glu Asp Leu Trp Leu Ser Pro Leu Thr
50 55 60

Met Glu Asp Leu Val Cys Tyr Ser Phe Gln Val Ala Arg Gly Met
65 70 75

Glu Phe Leu Ala Ser Arg Lys Cys Ile His Arg Asp Leu Ala Ala
80 85 90

Arg Asn Ile Leu Leu Ser Glu Ser Asp Val Val Lys Ile Cys Asp
95 100 105

Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp Pro Asp Tyr Val Arg
110 115 120

Lys Gly Ser Ala Arg Leu Pro Leu Lys Trp Met Ala Pro Glu Ser
125 130 135

Ile Phe Asp Lys Val Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe
140 145 150

Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser Pro Tyr
155 160 165

Pro Gly Val Gln Ile Asn Glu Glu Phe Cys Gln Arg Leu Arg Asp
170 175 180

Gly Thr Arg Met Arg Ala Pro Glu Leu Ala Thr Pro Ala Ile Arg
185 190 195

Arg Ile Met Leu Asn Cys Trp Ser Gly Asp Pro Lys Ala Arg Pro
200 205 210

Ala Phe Ser Glu Leu Val Glu Ile Leu Gly Asp Leu Leu Gln Gly
215 220 225

Arg Gly Leu Gln Glu Glu Glu Glu Val Cys Met Ala Pro Arg Ser
230 235 240

Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser Gln Val Ser Thr Met
245 250 255

Ala Leu His Ile Ala Gln Ala Asp Ala Glu Asp Ser Pro Pro Ser
260 265 270

Leu Gln Arg His Ser Leu Ala Ala Arg Tyr Tyr Asn Trp Val Ser
275 280 285

Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu Thr Arg Gly Ser Ser
290 295 300

Arg Met Lys Thr Phe Glu Glu Phe Pro Met Thr Pro Thr Thr Tyr
305 310 315

Lys Gly Ser Val Asp Asn Gln Thr Asp Ser Gly Met Val Leu Ala
320 325 330

Ser Glu Glu Cys Glu Gln Ile Glu Ser Arg Tyr Arg Gln Glu Ser
335 340 345

Gly Phe Arg
348

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7607 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA 700

TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACTTGGCT TCGTTAGAAC GCGGCTACAA TTAATACATA 800

ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA GAATAACATC 850

CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900

CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT 950

CGAGTCGACT TTTTTTTTTT TTTTTGTAGG CCAAAGGGTA CTTCTTTTTC 1000

TTTATTAATT ACTCAGAAGT CTAGGCCACA GCAATCTACT GTTCTCCTCT 1050

CATTTTCCTA AACTATTTTG ATACCTATTT CTCAGACTTT ATGGGCTATT 1100

AGACATTTCT CACATTTCCA TAGATAATAA CTCATCCGTT TTGCAACCTG 1150

ATTCTCAATA TTAAGAGATT AAAACTAATG TATATGACTC TCAGTTGACA 1200

CATACTGAAG TACAGAAAAA TTCCATCATT TCCTTCTGCA AAATGAAAAA 1250

GACTTCGTTT TCTCAACAGC TGCATCATTT TTTTATGCAT AGAAAAAAAT 1300

GTGCAATTAC TCCAAGTACA ATCAAGTCAT TTAACATGGC TTTACCATCA 1350

TTGTAGTTAC AGGATATTTT AAAAGAGAAA AAAAAATCTC AAAGCACAGG 1400

TCCTGCTGTG CAGCAAAGCA ATCAAATTCC TTCATAATAA CAGCCTGATG 1450

GGATTCAGCA ATCTGAGGAA TAATGAATAA CCACTCTAAT CAGTAAACAG 1500

GAAAATGCTA CAACAGTCAC TGAGTAAAAA TTGGACTATC ATCTGTTGAT 1550

TCTCTTGATC GACATTTCAA ACAATAAATG GAAATGTAAG TATCTCTTAA 1600

AAAGAAAAAT AACTTGGTTT AGTGTGCTTA ATTTTACCAG GCAGTGAGGA 1650

AATTATATAT CACCTTGACT GTCCTGCAGT GTTGCCCAGT CAATAAAATG 1700

CACAAATAAT CTTTTTCATA ATACATGGCC AACTTTATCC TATCACTTGA 1750

ATATGTCAGG ATAAACTGAT TGTGCAGTTG GTTGATAACA TTGTATTTTG 1800

GAATGGATTA TTTGAATTTG TTTTGCTACT TTATTATTTG ATATTCTTCT 1850

CCAGTGTTCA TCTTATGAAG TTATTTGCAT CTGAATATGA AGAGTCTGTT 1900

TCAAAATAGT CTTCAAGTTT CCAACGCAGT GTCTCAAATG TAGGTCGTTC 1950

CTTAGGCTCT GCATTCCAGC ACTCCAACAT GATGTTGTAA AATTGCTGTG 2000

GACAGTTGGA TGGTTGCGGA AGTCTATAGT TTTGAGCCAA CATCTGGATT 2050

ACCTGGGCAC CTGTCATACC ACTGTAAGGC ATTTTGCCAT AAGTAATGAT 2100

TTCATAAAGA AGGATTCCAA ATGACCATAC ATCGGACTTA ATGCTGAATT 2150

TATTACTACG AATGGCTTCG GGCGCAGTCC ACTTCACCGG CAGCTTTATT 2200

TCGTGTCTAG ATTCATAGAT GTCTTCATTA TCTACCTTAA AAACTCTGGC 2250

AAGTCCAAAA TCTGCTACTT TGTAGATATT ATGTTCACCA ACGAGGACAT 2300

TTCTGGCAGC CAGATCTCTG TGAATGTAGT TCCGAGACTC CAGATAGGCC 2350

ATTCCAGAGG CAACCTGTGC CGCCATGTCT ACCTGTTGAG TCAGATGGAT 2400

TTTTGATCCA GTGTCATTTT GGAGATATTC TTGCAGACTT CCATGTCTCA 2450

TCAACTCTGT AATAATATAA ATTGGATCTT CTAAAGTGCA AACAGCATAA 2500

AGCTGGATAA GCTTTGGATG TCTTAGGTTC TTCATTATCT GTGCCTCCCT 2550

CAGGAAGTCA TTTGGATCCA TTGAACCTGG TTTTAATGTT TTCACTGCTA 2600

CTGGAGTGGT ATTGTTCCAC AGACCTTCCC ATACTTCGCC AAACTGACCA 2650

GATCCCAATC GCTTCAGAAG CTGTATGGAG TTGCGGTCTA TCTCCCATTG 2700

GTCCACGGTT TTATACGACA AATCAAATGG AGCTGGGACC TGGATCTTTA 2750

AGCATGGTTT CCCCAGCTTG ACACACAGGC CGTCACTTGT CTTGGTGTAG 2800

TGGCTCACAA ATTCGTTCAG TGTTGAAAAG ATTCTTCTTC GCGTGAGAAA 2850

AAATCCCCCT TCATCCAGTC TTTTAATTCT GTAGTGTTTT ACAACTGCTC 2900

CATCTAAAAC TGAAAGAGAG AATTCTCCTT TTTGGCTTTC ACTTTCTCTG 2950

ATTAGAAAGG AACCGGTCTT GTTTTCTGAA TATAATAGTT GTTTCTCTGC 3000

ATCTGATCTT CCGATTGCTC CAAAGAACCA CGGCTCTGCC TGTAGGCTTC 3050

TGTCCTCAGC CACGTAGTTA GAAGGAATAT AGCCTTGTAG TTGCTGACTG 3100

GAGCCATCTC GTCTTTTCTC CAAGTGTCTG GCAAACCACC AGCCCTCATG 3150

CAAAGTGTCC AGAACTTGAA GTTTGTCACC TGCTCGGAAG CTCAAGTCCT 3200

CAGCAGTCCG AGCCTGGTAA TCAAACAAAG CCACAAAGTA GTGGCCATGC 3250

CTCTGTGACT GGGGAGAGCA AAGGGCCCCT GGATTTTCAA TCACGGTTGA 3300

CTTGTCTGCC TCCGTGGACA AACAGGGGAG ATAGGGTTCT AGGTACTCCC 3350

AGAGCCTCTG ACAGATGTTG CTCATTGTGC CTTGGTGGGG AGAAGAGGAG 3400

CAGGGCTTCT CCCTCTCCCC TTAGTCTCTG CGATCCACCT TATCTTCCTT 3450

CACCAGGCAA CTTTGAAGTC AGCACCAACT CACCATACTT CGGAGAGTAT 3500

GCAAAGTCCC GTTTCAGATC AGTCCAGCAG CTGGGTTGCA GCAAGTCCTA 3550

CCTGGAGAGA CTTACCGGCT TGCTTTCTGT GGCTGGAGGT GCTACCCCGA 3600

GGCAAAACTG AGCAGGAGCT GGGCAGCTGC TCACTAGGAA GGTGTCTTTT 3650

CTTCTTATCT GCTTAAGAAT CCCACAACAA AAATAAAATA AAATTAAAAG 3700

GGCTTTATTT AGACAAATAT CTGAGAACAG AATGGTGCCA TCTTGCCTTT 3750

TGTCCCAATA AAAAGTTAGC AAGAGGAAGC TACTAACCCC TGGTAAAACC 3800

TCCACGTCTT GCTTTCGCCA GGGTCGACTC GAGGGATCTT CCATACCTAC 3850

CAGTTCTGCG CCTGCAGGTC GCGGCCGCGA CTCTAGAGTC GACCTGCAGA 3900

AGCTTGGCCG CCATGGCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA 3950

AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACTG 4000

CATTCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG 4050

GATCGGGAAT TAATTCGGCG CAGCACCATG GCCTGAAATA ACCTCTGAAA 4100

GAGGAACTTG GTTAGGTACC TTCTGAGGCG GAAAGAACCA GCTGTGGAAT 4150

GTGTGTCAGT TAGGGTGTGG AAAGTCCCCA GGCTCCCCAG CAGGCAGAAG 4200

TATGCAAAGC ATGCATCTCA ATTAGTCAGC AACCAGGTGT GGAAAGTCCC 4250

CAGGCTCCCC AGCAGGCAGA AGTATGCAAA GCATGCATCT CAATTAGTCA 4300

GCAACCATAG TCCCGCCCCT AACTCCGCCC ATCCCGCCCC TAACTCCGCC 4350

CAGTTCCGCC CATTCTCCGC CCCATGGCTG ACTAATTTTT TTTATTTATG 4400

CAGAGGCCGA GGCCGCCTCG GCCTCTGAGC TATTCCAGAA GTAGTGAGGA 4450

GGCTTTTTTG GAGGCCTAGG CTTTTGCAAA AAGCTGTTAA CAGCTTGGCA 4500

CTGGCCGTCG TTTTACAACG TCGTGACTGG GAAAACCCTG GCGTTACCCA 4550

ACTTAATCGC CTTGCAGCAC ATCCCCCTTT CGCCAGCTGG CGTAATAGCG 4600

AAGAGGCCCG CACCGATCGC CCTTCCCAAC AGTTGCGCAG CCTGAATGGC 4650

GAATGGCGCC TGATGCGGTA TTTTCTCCTT ACGCATCTGT GCGGTATTTC 4700

ACACCGCATA CGTCAAAGCA ACCATAGTAC GCGCCCTGTA GCGGCGCATT 4750

AAGCGCGGCG GGTGTGGTGG TTACGCGCAG CGTGACCGCT ACACTTGCCA 4800

GCGCCCTAGC GCCCGCTCCT TTCGCTTTCT TCCCTTCCTT TCTCGCCACG 4850

TTCGCCGGCT TTCCCCGTCA AGCTCTAAAT CGGGGGCTCC CTTTAGGGTT 4900

CCGATTTAGT GCTTTACGGC ACCTCGACCC CAAAAAACTT GATTTGGGTG 4950

ATGGTTCACG TAGTGGGCCA TCGCCCTGAT AGACGGTTTT TCGCCCTTTG 5000

ACGTTGGAGT CCACGTTCTT TAATAGTGGA CTCTTGTTCC AAACTGGAAC 5050

AACACTCAAC CCTATCTCGG GCTATTCTTT TGATTTATAA GGGATTTTGC 5100

CGATTTCGGC CTATTGGTTA AAAAATGAGC TGATTTAACA AAAATTTAAC 5150

GCGAATTTTA ACAAAATATT AACGTTTACA ATTTTATGGT GCACTCTCAG 5200

TACAATCTGC TCTGATGCCG CATAGTTAAG CCAGCCCCGA CACCCGCCAA 5250

CACCCGCTGA CGCGCCCTGA CGGGCTTGTC TGCTCCCGGC ATCCGCTTAC 5300

AGACAAGCTG TGACCGTCTC CGGGAGCTGC ATGTGTCAGA GGTTTTCACC 5350

GTCATCACCG AAACGCGCGA GACGAAAGGG CCTCGTGATA CGCCTATTTT 5400

TATAGGTTAA TGTCATGATA ATAATGGTTT CTTAGACGTC AGGTGGCACT 5450

TTTCGGGGAA ATGTGCGCGG AACCCCTATT TGTTTATTTT TCTAAATACA 5500

TTCAAATATG TATCCGCTCA TGAGACAATA ACCCTGATAA ATGCTTCAAT 5550

AATATTGAAA AAGGAAGAGT ATGAGTATTC AACATTTCCG TGTCGCCCTT 5600

ATTCCCTTTT TTGCGGCATT TTGCCTTCCT GTTTTTGCTC ACCCAGAAAC 5650

GCTGGTGAAA GTAAAAGATG CTGAAGATCA GTTGGGTGCA CGAGTGGGTT 5700

ACATCGAACT GGATCTCAAC AGCGGTAAGA TCCTTGAGAG TTTTCGCCCC 5750

GAAGAACGTT TTCCAATGAT GAGCACTTTT AAAGTTCTGC TATGTGGCGC 5800

GGTATTATCC CGTATTGACG CCGGGCAAGA GCAACTCGGT CGCCGCATAC 5850

ACTATTCTCA GAATGACTTG GTTGAGTACT CACCAGTCAC AGAAAAGCAT 5900

CTTACGGATG GCATGACAGT AAGAGAATTA TGCAGTGCTG CCATAACCAT 5950

GAGTGATAAC ACTGCGGCCA ACTTACTTCT GACAACGATC GGAGGACCGA 6000

AGGAGCTAAC CGCTTTTTTG CACAACATGG GGGATCATGT AACTCGCCTT 6050

GATCGTTGGG AACCGGAGCT GAATGAAGCC ATACCAAACG ACGAGCGTGA 6100

CACCACGATG CCTGTAGCAA TGGCAACAAC GTTGCGCAAA CTATTAACTG 6150

GCGAACTACT TACTCTAGCT TCCCGGCAAC AATTAATAGA CTGGATGGAG 6200

GCGGATAAAG TTGCAGGACC ACTTCTGCGC TCGGCCCTTC CGGCTGGCTG 6250

GTTTATTGCT GATAAATCTG GAGCCGGTGA GCGTGGGTCT CGCGGTATCA 6300

TTGCAGCACT GGGGCCAGAT GGTAAGCCCT CCCGTATCGT AGTTATCTAC 6350

ACGACGGGGA GTCAGGCAAC TATGGATGAA CGAAATAGAC AGATCGCTGA 6400

GATAGGTGCC TCACTGATTA AGCATTGGTA ACTGTCAGAC CAAGTTTACT 6450

CATATATACT TTAGATTGAT TTAAAACTTC ATTTTTAATT TAAAAGGATC 6500

TAGGTGAAGA TCCTTTTTGA TAATCTCATG ACCAAAATCC CTTAACGTGA 6550

GTTTTCGTTC CACTGAGCGT CAGACCCCGT AGAAAAGATC AAAGGATCTT 6600

CTTGAGATCC TTTTTTTCTG CGCGTAATCT GCTGCTTGCA AACAAAAAAA 6650

CCACCGCTAC CAGCGGTGGT TTGTTTGCCG GATCAAGAGC TACCAACTCT 6700

TTTTCCGAAG GTAACTGGCT TCAGCAGAGC GCAGATACCA AATACTGTTC 6750

TTCTAGTGTA GCCGTAGTTA GGCCACCACT TCAAGAACTC TGTAGCACCG 6800

CCTACATACC TCGCTCTGCT AATCCTGTTA CCAGTGGCTG CTGCCAGTGG 6850

CGATAAGTCG TGTCTTACCG GGTTGGACTC AAGACGATAG TTACCGGATA 6900

AGGCGCAGCG GTCGGGCTGA ACGGGGGGTT CGTGCACACA GCCCAGCTTG 6950

GAGCGAACGA CCTACACCGA ACTGAGATAC CTACAGCGTG AGCTATGAGA 7000

AAGCGCCACG CTTCCCGAAG GGAGAAAGGC GGACAGGTAT CCGGTAAGCG 7050

GCAGGGTCGG AACAGGAGAG CGCACGAGGG AGCTTCCAGG GGGAAACGCC 7100

TGGTATCTTT ATAGTCCTGT CGGGTTTCGC CACCTCTGAC TTGAGCGTCG 7150

ATTTTTGTGA TGCTCGTCAG GGGGGCGGAG CCTATGGAAA AACGCCAGCA 7200

ACGCGGCCTT TTTACGGTTC CTGGCCTTTT GCTGGCCTTT TGCTCACATG 7250

TTCTTTCCTG CGTTATCCCC TGATTCTGTG GATAACCGTA TTACCGCCTT 7300

TGAGTGAGCT GATACCGCTC GCCGCAGCCG AACGACCGAG CGCAGCGAGT 7350

CAGTGAGCGA GGAAGCGGAA GAGCGCCCAA TACGCAAACC GCCTCTCCCC 7400

GCGCGTTGGC CGATTCATTA ATGCAGCTGG CACGACAGGT TTCCCGACTG 7450

GAAAGCGGGC AGTGAGCGCA ACGCAATTAA TGTGAGTTAG CTCACTCATT 7500

AGGCACCCCA GGCTTTACAC TTTATGCTTC CGGCTCGTAT GTTGTGTGGA 7550

ATTGTGAGCG GATAACAATT TCACACAGGA AACAGCTATG ACATGATTAC 7600

GAATTAA 7607

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 505 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Ser Asn Ile Cys Gln Arg Leu Trp Glu Tyr Leu Glu Pro Tyr
1 5 10 15

Leu Pro Cys Leu Ser Thr Glu Ala Asp Lys Ser Thr Val Ile Glu
20 25 30

Asn Pro Gly Ala Leu Cys Ser Pro Gln Ser Gln Arg His Gly His
35 40 45

Tyr Phe Val Ala Leu Phe Asp Tyr Gln Ala Arg Thr Ala Glu Asp
50 55 60

Leu Ser Phe Arg Ala Gly Asp Lys Leu Gln Val Leu Asp Thr Leu
65 70 75

```
His Glu Gly Trp Trp Phe Ala Arg His Leu Glu Lys Arg Arg Asp
                  80                  85                  90

Gly Ser Ser Gln Gln Leu Gln Gly Tyr Ile Pro Ser Asn Tyr Val
                  95                 100                 105

Ala Glu Asp Arg Ser Leu Gln Ala Glu Pro Trp Phe Phe Gly Ala
                 110                 115                 120

Ile Gly Arg Ser Asp Ala Glu Lys Gln Leu Leu Tyr Ser Glu Asn
                 125                 130                 135

Lys Thr Gly Ser Phe Leu Ile Arg Glu Ser Glu Ser Gln Lys Gly
                 140                 145                 150

Glu Phe Ser Leu Ser Val Leu Asp Gly Ala Val Val Lys His Tyr
                 155                 160                 165

Arg Ile Lys Arg Leu Asp Glu Gly Gly Phe Phe Leu Thr Arg Arg
                 170                 175                 180

Arg Ile Phe Ser Thr Leu Asn Glu Phe Val Ser His Tyr Thr Lys
                 185                 190                 195

Thr Ser Asp Gly Leu Cys Val Lys Leu Gly Lys Pro Cys Leu Lys
                 200                 205                 210

Ile Gln Val Pro Ala Pro Phe Asp Leu Ser Tyr Lys Thr Val Asp
                 215                 220                 225

Gln Trp Glu Ile Asp Arg Asn Ser Ile Gln Leu Leu Lys Arg Leu
                 230                 235                 240

Gly Ser Gly Gln Phe Gly Glu Val Trp Glu Gly Leu Trp Asn Asn
                 245                 250                 255

Thr Thr Pro Val Ala Val Lys Thr Leu Lys Pro Gly Ser Met Asp
                 260                 265                 270

Pro Asn Asp Phe Leu Arg Glu Ala Gln Ile Met Lys Asn Leu Arg
                 275                 280                 285

His Pro Lys Leu Ile Gln Leu Tyr Ala Val Cys Thr Leu Glu Asp
                 290                 295                 300

Pro Ile Tyr Ile Ile Thr Glu Leu Met Arg His Gly Ser Leu Gln
                 305                 310                 315

Glu Tyr Leu Gln Asn Asp Thr Gly Ser Lys Ile His Leu Thr Gln
                 320                 325                 330

Gln Val Asp Met Ala Ala Gln Val Ala Ser Gly Met Ala Tyr Leu
                 335                 340                 345

Glu Ser Arg Asn Tyr Ile His Arg Asp Leu Ala Ala Arg Asn Val
                 350                 355                 360
```

Leu Val Gly Glu His Asn Ile Tyr Lys Val Ala Asp Phe Gly Leu
365 370 375

Ala Arg Val Phe Lys Val Asp Asn Glu Asp Ile Tyr Glu Ser Arg
380 385 390

His Glu Ile Lys Leu Pro Val Lys Trp Thr Ala Pro Glu Ala Ile
395 400 405

Arg Ser Asn Lys Phe Ser Ile Lys Ser Asp Val Trp Ser Phe Gly
410 415 420

Ile Leu Leu Tyr Glu Ile Ile Thr Tyr Gly Lys Met Pro Tyr Ser
425 430 435

Gly Met Thr Gly Ala Gln Val Ile Gln Met Leu Ala Gln Asn Tyr
440 445 450

Arg Leu Pro Gln Pro Ser Asn Cys Pro Gln Gln Phe Tyr Asn Ile
455 460 465

Met Leu Glu Cys Trp Asn Ala Glu Pro Lys Glu Arg Pro Thr Phe
470 475 480

Glu Thr Leu Arg Trp Lys Leu Glu Asp Tyr Phe Glu Thr Asp Ser
485 490 495

Ser Tyr Ser Asp Ala Asn Asn Phe Ile Arg
500 505

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 404 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GCGGCCGCAG AGAAAGCAGA GGATGGGGCT TAGCAGCTGG CAGAGCCAGG 50

AGCGGGGAGG TAGCAGAAAG ACCACAAGTA CAAAGAAGTC CTGAAACTTT 100

GGTTTTGCTG CTGCAGCCCA TTGAGAGTGA CGACATGGAG CACAAGACCC 150

TGAAGATCAC CGACTTTGGC CTGGCCCGAG AGTGGCACAA AACCACACAA 200

ATGAGTGCCG CNGGCACCTA CNCCTGGATG GCTCCTGAGG TTATCAAGGC 250

CTCCACCTTC TCTAAGGGCA GTGACGTCTG GAGTTTTGGG GTGCTGCTGT 300

GGGAACTGCT GACCGGGGAG NTGCCATACC GTGGCATTGA CTGCCTTGCT 350

GTGGCCTATG GCGTAGCTGT TAACAAGCTC ACACTGCCAT CCATCCACCT 400

GGCC 404

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3120 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

ATGAGAGCGT TGGCGCGCGA CGGCGGCCAG CTGCCGCTGC TCGTTGTTTT 50

TTCTGCAATG ATATTTGGGA CTATTACAAA TCAAGATCTG CCTGTGATCA 100

AGTGTGTTTT AATCAATCAT AAGAACAATG ATTCATCAGT GGGGAAGTCA 150

TCATCATATC CCATGGTATC AGAATCCCCG GAAGACCTCG GGTGTGCGTT 200

GAGACCCCAG AGCTCAGGGA CAGTGTACGA AGCTGCCGCT GTGGAAGTGG 250

ATGTATCTGC TTCCATCACA CTGCAAGTGC TGGTCGATGC CCCAGGGAAC 300

ATTTCCTGTC TCTGGGTCTT TAAGCACAGC TCCCTGAATT GCCAGCCACA 350

TTTTGATTTA CAAAACAGAG GAGTTGTTTC CATGGTCATT TTGAAAATGA 400

CAGAAACCCA AGCTGGAGAA TACCTACTTT TTATTCAGAG TGAAGCTACC 450

AATTACACAA TATTGTTTAC AGTGAGTATA AGAAATACCC TGCTTTACAC 500

ATTAAGAAGA CCTTACTTTA GAAAAATGGA AAACCAGGAC GCCCTGGTCT 550

GCATATCTGA GAGCGTTCCA GAGCGGATCC TGGAATGGGT GCTTTGCGAT 600

TCACAGGGGG AAAGCTGTAA AGAAGAAAGT CCAGCTGTTG TTAAAAAGGA 650

GGAAAAAGTG CTTCATGAAT TATTTGGGAC GGACATAAGG TGCTGTGCCA 700

GAAATGAACT GGGCAGGGAA TGCACCAGGC TGTTCACAAT AGATCTAAAT 750

CAAACTCCTC AGACCACATT GCCACAATTA TTTCTTAAAG TAGGGGAACC 800

CTTATGGATA AGGTGCAAAG CTGTTCATGT GAACCATGGA TTCGGGCTCA 850

CCTGGGAATT AGAAAACAAA GCACTCGAGG AGGGCAACTA CTTTGAGATG 900

AGTACCTATT CAACAAACAG AACTATGATA CGGATTCTGT TTGCTTTTGT 950

ATCATCAGTG GCAAGAAACG ACACCGGATA CTACACTTGT TCCTCTTCAA 1000

AGCATCCCAG TCAATCAGCT TTGGTTACCA TCGTAGAAAA GGGATTTATA 1050

AATGCTACCA ATTCAAGTGA AGATTATGAA ATTGACCAAT ATGAAGAGTT 1100

TTGTTTTTCT GTCAGGTTTA AAGCCTACCC ACAAATCAGA TGTACGTGGA 1150

CCTTCTCTCG AAAATCATTT CCTTGTGAGC AAAAGGGTCT TGATAACGGA 1200

TACAGCATAT CCAAGTTTTG CAATCATAAG CACCAGCCAG GAGAATATAT 1250

ATTCCATGCA GAAAATGATG ATGCCCAATT TACCAAAATG TTCACGCTGT 1300

ATATAAGAAG GAAACCTCAA GTCCTCGCAG AAGCTTCGGC AAGTCAGGCG 1350

TCCTGTTTCT CGGATGGATA CCCATTACCA TCTTGGACCT GGAAGAAGTG 1400

TTCAGACAAG TCTCCCAACT GCACAGAAGA GATCACAGAA GGAGTCTGGA 1450

ATAGAAAGGC TAACAGAAAA GTGTTTGGAC AGTGGGTGTC GAGCAGTACT 1500

CTAAACATGA GTGAAGCCAT AAAAGGGTTC CTGGTCAAGT GCTGTGCATA 1550

CAATTCCCTT GGCACATCTT GTGAGACGAT CCTTTTAAAC TCTCCAGGCC 1600

CCTTCCCTTT CATCCAAGAC AACATCTCAT TCTATGCAAC AATTGGTGTT 1650

TGTCTCCTCT TCATTGTCGT TTTAACCCTG CTAATTTGTC ACAAGTACAA 1700

AAAGCAATTT AGGTATGAAA GCCAGCTACA GATGGTACAG GTGACCGGAT 1750

CCTCAGATTA TGAGTACTTC TACGTTGATT TCAGAGAATA TGAATATGAT 1800

GTCAAATGGG AGTTTCCAAG AGAAAATTTA GAGTTTGGGA AGGTACTAGG 1850

ATCAGGTGCT TTTGGAAAAG TGATGAACGC AACAGCTTAT GGAATTAGCA 1900

AAACAGGAGT CTCAATCCAG GTTACCGTCA AAATGCTGAA AGAAAAAGCA 1950

GACAGCTCTG AAAGAGAGGC ACTCATGTCA GAACTCAAGA TGATGACCCA 2000

GCTGGGAAGC CACGAGAATA TTGTGAACCT GCTGGGGGCG TGCACACTGT 2050

CAGGACCAAT TTACTTGATT TTTGAATACT GTTGCTATGG TGATCTTCTC 2100

AACTATCTAA GAAGTAAAAG AGAAAAATTT CACAGGACTT GGACAGAGAT 2150

TTTCAAGGAA CACAATTTCA GTTTTTACCC CACTTTCCAA TCACATCCAA 2200

ATTCCAGCAT GCCTGGTTCA AGAGAAGTTC AGATACACCC GGACTCGGAT 2250

CAAATCTCAG GGCTTCATGG GAATTCATTT CACTCTGAAG ATGAAATTGA 2300

ATATGAAAAC CAAAAAAGGC TGGAAGAAGA GGAGGACTTG AATGTGCTTA 2350

CATTTGAAGA TCTTCTTTGC TTTGCATATC AAGTTGCCAA AGGAATGGAA 2400

TTTCTGGAAT TTAAGTCGTG TGTTCACAGA GACCTGGCCG CCAGGAACGT 2450

GCTTGTCACC CACGGGAAAG TGGTGAAGAT ATGTGACTTT GGATTGGCTC 2500

GAGATATCAT GAGTGATTCC AACTATGTTG TCAGGGGCAA TGCCCGTCTG 2550

CCTGTAAAAT GGATGGCCCC CGAAAGCCTG TTTGAAGGCA TCTACACCAT 2600

TAAGAGTGAT GTCTGGTCAT ATGGAATATT ACTGTGGGAA ATCTTCTCAC 2650

TTGGTGTGAA TCCTTACCCT GGCATTCCGG TTGATGCTAA CTTCTACAAA 2700

CTGATTCAAA ATGGATTTAA AATGGATCAG CCATTTTATG CTACAGAAGA 2750

AATATACATT ATAATGCAAT CCTGCTGGGC TTTTGACTCA AGGAAACGGC 2800

CATCCTTCCC TAATTTGACT TCGTTTTTAG GATGTCAGCT GGCAGATGCA 2850

GAAGAAGCGA TGTATCAGAA TGTGGATGGC CGTGTTTCGG AATGTCCTCA 2900

CACCTACCAA AACAGGCGAC CTTTCAGCAG AGAGATGGAT TTGGGGCTAC 2950

TCTCTCCGCA GGCTCAGGTC GAAGATTCGT AGAGGAACAA TTTAGTTTTA 3000

AGGACTTCAT CCCTCCACCT ATCCCTAACA GGCTGTAGAT TACCAAAACA 3050

AGGTTAATTT CATCACTAAA AGAAAATCTA TTATCAACTG CTGCTTCACC 3100

AGACTTTTCT CTAGAGAGCG 3120

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3969 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCGGCGTCCA CCCGCCCAGG GAGAGTCAGA CCTGGGGGGG CGAGGGCCCC 50

CCAAACTCAG TTCGGATCCT ACCCGAGTGA GGCGGCGCCA TGGAGCTCCG 100

GGTGCTGCTC TGCTGGGCTT CGTTGGCCGC AGCTTTGGAA GAGACCCTGC 150

TGAACACAAA ATTGGAAACT GCTGATCTGA AGTGGGTGAC ATTCCCTCAG 200

GTGGACGGGC AGTGGGAGGA ACTGAGCGGC CTGGATGAGG AACAGCACAG 250

CGTGCGCACC TACGAAGTGT GTGACGTGCA GCGTGCCCCG GGCCAGGCCC 300

ACTGGCTTCG CACAGGTTGG GTCCCACGGC GGGGCGCCGT CCACGTGTAC 350

GCCACGCTGC GCTTCACCAT GCTCGAGTGC CTGTCCCTGC CTCGGGCTGG 400

GCGCTCCTGC AAGGAGACCT TCACCGTCTT CTACTATGAG AGCGATGCGG 450

ACACGGCCAC GGCCCTCACG CCAGCCTGGA TGGAGAACCC CTACATCAAG 500

GTGGACACGG TGGCCGCGGA GCATCTCACC CGGAAGCGCC CTGGGGCCGA 550

GGCCACCGGG AAGGTGAATG TCAAGACGCT GCGTCTGGGA CCGCTCAGCA 600

AGGCTGGCTT CTACCTGGCC TTCCAGGACC AGGGTGCCTG CATGGCCCTG 650

CTATCCCTGC ACCTCTTCTA CAAAAAGTGC GCCCAGCTGA CTGTGAACCT 700

GACTCGATTC CCGGAGACTG TGCCTCGGGA GCTGGTTGTG CCCGTGGCCG 750

GTAGCTGCGT GGTGGATGCC GTCCCCGCCC CTGGCCCCAG CCCCAGCCTC 800

TACTGCCGTG AGGATGGCCA GTGGGCCGAA CAGCCGGTCA CGGGCTGCAG 850

CTGTGCTCCG GGGTTCGAGG CAGCTGAGGG GAACACCAAG TGCCGAGCCT 900

GTGCCCAGGG CACCTTCAAG CCCCTGTCAG GAGAAGGGTC CTGCCAGCCA 950

TGCCCAGCCA ATAGCCACTC TAACACCATT GGATCAGCCG TCTGCCAGTG 1000

CCGCGTCGGG TACTTCCGGG CACGCACAGA CCCCCGGGGT GCACCCTGCA 1050

CCACCCCTCC TTCGGCTCCG CGGAGCGTGG TTTCCCGCCT GAACGGCTCC 1100

TCCCTGCACC TGGAATGGAG TGCCCCCCTG GAGTCTGGTG GCCGAGAGGA 1150

CCTCACCTAC GCCCTCCGCT GCCGGGAGTG CCGACCCGGA GGCTCCTGTG 1200

CGCCCTGCGG GGGAGACCTG ACTTTTGACC CCGGCCCCCG GGACCTGGTG 1250

GAGCCCTGGG TGGTGGTTCG AGGGCTACGT CCTGACTTCA CCTATACCTT 1300

TGAGGTCACT GCATTGAACG GGGTATCCTC CTTAGCCACG GGGCCCGTCC 1350

CATTTGAGCC TGTCAATGTC ACCACTGACC GAGAGGTACC TCCTGCAGTG 1400

TCTGACATCC GGGTGACGCG GTCCTCACCC AGCAGCTTGA GCCTGGCCTG 1450

GGCTGTTCCC CGGGCACCCA GTGGGGCTGT GCTGGACTAC GAGGTCAAAT 1500

ACCATGAGAA GGGCGCCGAG GGTCCCAGCA GCGTGCGGTT CCTGAAGACG 1550

TCAGAAAACC GGGCAGAGCT GCGGGGGCTG AAGCGGGGAG CCAGCTACCT 1600

GGTGCAGGTA CGGGCGCGCT CTGAGGCCGG CTACGGGCCC TTCGGCCAGG 1650

AACATCACAG CCAGACCCAA CTGGATGAGA GCGAGGGCTG GCGGGAGCAG 1700

CTGGCCCTGA TTGCGGGCAC GGCAGTCGTG GGTGTGGTCC TGGTCCTGGT 1750

GGTCATTGTG GTCGCAGTTC TCTGCCTCAG GAAGCAGAGC AATGGGAGAG 1800

AAGCAGAATA TTCGGACAAA CACGGACAGT ATCTCATCGG ACATGGTACT 1850

AAGGTCTACA TCGACCCCTT CACTTATGAA GACCCTAATG AGGCTGTGAG 1900

GGAATTTGCA AAAGAGATCG ATGTCTCCTA CGTCAAGATT GAAGAGGTGA 1950

TTGGTGCAGG TGAGTTTGGC GAGGTGTGCC GGGGGCGGCT CAAGGCCCCA 2000

GGGAAGAAGG AGAGCTGTGT GGCAATCAAG ACCCTGAAGG GTGGCTACAC 2050

GGAGCGGCAG CGGCGTGAGT TTCTGAGCGA GGCCTCCATC ATGGGCCAGT 2100

TCGAGCACCC CAATATCATC CGCCTGGAGG GCGTGGTCAC CAACAGCATG 2150

CCCGTCATGA TTCTCACAGA GTTCATGGAG AACGGCGCCC TGGACTCCTT 2200

CCTGCGGCTA AACGACGGAC AGTTCACAGT CATCCAGCTC GTGGGCATGC 2250

TGCGGGGCAT CGCCTCGGGC ATGCGGTACC TTGCCGAGAT GAGCTACGTC 2300

CACCGAGACC TGGCTGCTCG CAACATCCTA GTCAACAGCA ACCTCGTCTG 2350

CAAAGTGTCT GACTTTGGCC TTTCCCGATT CCTGGAGGAG AACTCTTCCG 2400

ATCCCACCTA CACGAGCTCC CTGGGAGGAA AGATTCCCAT CCGATGGACT 2450

GCCCCGGAGG CCATTGCCTT CCGGAAGTTC ACTTCCGCCA GTGATGCCTG 2500

GAGTTACGGG ATTGTGATGT GGGAGGTGAT GTCATTTGGG GAGAGGCCGT 2550

ACTGGGACAT GAGCAATCAG GACGTGATCA ATGCCATTGA ACAGGACTAC 2600

CGGCTGCCCC CGCCCCCAGA CTGTCCCACC TCCCTCCACC AGCTCATGCT 2650

GGACTGTTGG CAGAAAGACC GGAATGCCCG GCCCCGCTTC CCCCAGGTGG 2700

TCAGCGCCCT GGACAAGATG ATCCGGAACC CCGCCAGCCT CAAAATCGTG 2750

GCCCGGGAGA ATGGCGGGGC CTCACACCCT CTCCTGGACC AGCGGCAGCC 2800

TCACTACTCA GCTTTTGGCT CTGTGGGCGA GTGGCTTCGG GCCATCAAAA 2850

TGGGAAGATA CGAAGAAAGT TTCGCAGCCG CTGGCTTTGG CTCCTTCGAG 2900

CTGGTCAGCC AGATCTCTGC TGAGGACCTG CTCCGAATCG GAGTCACTCT 2950

GGCGGGACAC CAGAAGAAAA TCTTGGCCAG TGTCCAGCAC ATGAAGTCCC 3000

AGGCCAAGCC GGGAACCCCG GGTGGGACAG GAGGACCGGC CCCGCAGTAC 3050

TGACCTGCAG GAACTCCCCA CCCCAGGGAC ACCGCCTCCC CATTTTCCGG 3100

GGCAGAGTGG GGACTCACAG AGGCCCCCAG CCCTGTGCCC CGCTGGATTG 3150

CACTTTGAGC CCGTGGGGTG AGGAGTTGGC AATTTGGAGA GACAGGATTT 3200

GGGGGTTCTG CCATAATAGG AGGGGAAAAT CACCCCCCAG CCACCTCGGG 3250

GAACTCCAGA CCAAGGGTGA GGGCGCCTTT CCCTCAGGAC TGGGTGTGAC 3300

CAGAGGAAAA GGAAGTGCCC AACATCTCCC AGCCTCCCCA GGTGCCCCCC 3350

TCACCTTGAT GGGTGCGTTC CCGCAGACCA AAGAGAGTGT GACTCCCTTG 3400

CCAGCTCCAG AGTGGGGGGG CTGTCCCAGG GGGCAAGAAG GGGTGTCAGG 3450

GCCCAGTGAC AAAATCATTG GGGTTTGTAG TCCCAACTTG CTGCTGTCAC 3500

CACCAAACTC AATCATTTTT TTCCCTTGTA AATGCCCCTC CCCCAGCTGC 3550

TGCCTTCATA TTGAAGGTTT TTGAGTTTTG TTTTTGGTCT TAATTTTTCT 3600

CCCCGTTCCC TTTTTGTTTC TTCGTTTTGT TTTTCTACCG TCCTTGTCAT 3650

AACTTTGTGT TGGAGGGAAC CTGTTTCACT ATGGCCTCCT TTGCCCAAGT 3700

TGAAACAGGG GCCCATCATC ATGTCTGTTT CCAGAACAGT GCCTTGGTCA 3750

TCCCACATCC CCGGACCCCG CCTGGGACCC CCAAGCTGTG TCCTATGAAG 3800

GGGTGTGGGG TGAGGTAGTG AAAAGGGCGG TAGTTGGTGG TGGAACCCAG 3850

AAACGGACGC CGGTGCTTGG AGGGGTTCTT AAATTATATT TAAAAAAGTA 3900

ACTTTTTGTA TAAATAAAAG AAAATGGGAC GTGTCCCAGC TCCAGGGGTA 3950

AAAAAAAAAA AAAAAAAAA 3969

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1276 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala
1 5 10 15

Leu Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu
20 25 30

Lys Trp Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu
35 40 45

Ser Gly Leu Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val
50 55 60

Cys Asp Val Gln Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr
65 70 75

Gly Trp Val Pro Arg Arg Gly Ala Val His Val Tyr Ala Thr Leu
80 85 90

Arg Phe Thr Met Leu Glu Cys Leu Ser Leu Pro Arg Ala Gly Arg
95 100 105

Ser Cys Lys Glu Thr Phe Thr Val Phe Tyr Tyr Glu Ser Asp Ala
110 115 120

Asp Thr Ala Thr Ala Leu Thr Pro Ala Trp Met Glu Asn Pro Tyr
125 130 135

Ile Lys Val Asp Thr Val Ala Ala Glu His Leu Thr Arg Lys Arg
140 145 150

Pro Gly Ala Glu Ala Thr Gly Lys Val Asn Val Lys Thr Leu Arg
155 160 165

Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu Ala Phe Gln Asp
170 175 180

Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu Phe Tyr Lys
185 190 195

Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro Glu Thr
200 205 210

Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val Val
215 220 225

Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg
230 235 240

Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys
245 250 255

Ala Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala
260 265 270

Cys Ala Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys
275 280 285

Gln Pro Cys Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala
290 295 300

Val Cys Gln Cys Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro
305 310 315

Arg Gly Ala Pro Cys Thr Thr Pro Pro Ser Ala Pro Arg Ser Val
320 325 330

Val Ser Arg Leu Asn Gly Ser Ser Leu His Leu Glu Trp Ser Ala
335 340 345

Pro Leu Glu Ser Gly Gly Arg Glu Asp Leu Thr Tyr Ala Leu Arg
350 355 360

Cys Arg Glu Cys Arg Pro Gly Gly Ser Cys Ala Pro Cys Gly Gly
365 370 375

Asp Leu Thr Phe Asp Pro Gly Pro Arg Asp Leu Val Glu Pro Trp
380 385 390

Val Val Val Arg Gly Leu Arg Pro Asp Phe Thr Tyr Thr Phe Glu
395 400 405

Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala Thr Gly Pro Val
410 415 420

Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu Val Pro Pro
425 430 435

Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser Ser Leu
440 445 450

Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Val Leu
455 460 465

Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser
470 475 480

Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg
485 490 495

Gly Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg
500 505 510

Ser Glu Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln
515 520 525

Thr Gln Leu Asp Glu Ser Glu Gly Trp Arg Glu Gln Leu Ala Leu
530 535 540

Ile Ala Gly Thr Ala Val Val Gly Val Val Leu Val Leu Val Val
545 550 555

Ile Val Val Ala Val Leu Cys Leu Arg Lys Gln Ser Asn Gly Arg
560 565 570

Glu Ala Glu Tyr Ser Asp Lys His Gly Gln Tyr Leu Ile Gly His
575 580 585

Gly Thr Lys Val Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn
590 595 600

Glu Ala Val Arg Glu Phe Ala Lys Glu Ile Asp Val Ser Tyr Val
605 610 615

Lys Ile Glu Glu Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys
620 625 630

Arg Gly Arg Leu Lys Ala Pro Gly Lys Lys Glu Ser Cys Val Ala
635 640 645

Ile Lys Thr Leu Lys Gly Gly Tyr Thr Glu Arg Gln Arg Arg Glu
650 655 660

Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Glu His Pro Asn
665 670 675

Ile Ile Arg Leu Glu Gly Val Val Thr Asn Ser Met Pro Val Met
680 685 690

Ile Leu Thr Glu Phe Met Glu Asn Gly Ala Leu Asp Ser Phe Leu
695 700 705

Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met
710 715 720

Leu Arg Gly Ile Ala Ser Gly Met Arg Tyr Leu Ala Glu Met Ser
725 730 735

Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser
740 745 750

Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu
755 760 765

Glu Glu Asn Ser Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly
770 775 780

Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Phe Arg
785 790 795

Lys Phe Thr Ser Ala Ser Asp Ala Trp Ser Tyr Gly Ile Val Met
800 805 810

Trp Glu Val Met Ser Phe Gly Glu Arg Pro Tyr Trp Asp Met Ser
815 820 825

Asn Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro
830 835 840

Pro Pro Pro Asp Cys Pro Thr Ser Leu His Gln Leu Met Leu Asp
845 850 855

Cys Trp Gln Lys Asp Arg Asn Ala Arg Pro Arg Phe Pro Gln Val
860 865 870

Val Ser Ala Leu Asp Lys Met Ile Arg Asn Pro Ala Ser Leu Lys
875 880 885

Ile Val Ala Arg Glu Asn Gly Gly Ala Ser His Pro Leu Leu Asp
890 895 900

Gln Arg Gln Pro His Tyr Ser Ala Phe Gly Ser Val Gly Glu Trp
905 910 915

Leu Arg Ala Ile Lys Met Gly Arg Tyr Glu Glu Ser Phe Ala Ala
920 925 930

Ala Gly Phe Gly Ser Phe Glu Leu Val Ser Gln Ile Ser Ala Glu
935 940 945

Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln Lys Lys
950 955 960

Ile Leu Ala Ser Val Gln His Met Lys Ser Gln Ala Lys Pro Gly
965 970 975

Thr Pro Gly Gly Thr Gly Gly Pro Ala Pro Gln Tyr Pro Ala Gly
980 985 990

Thr Pro His Pro Arg Asp Thr Ala Ser Pro Phe Ser Gly Ala Glu
995 1000 1005

Trp Gly Leu Thr Glu Ala Pro Ser Pro Val Pro Arg Trp Ile Ala
1010 1015 1020

Leu Ala Arg Gly Val Arg Ser Trp Gln Phe Gly Glu Thr Gly Phe
1025 1030 1035

Gly Gly Ser Ala Ile Ile Gly Gly Glu Asn His Pro Pro Ala Thr
1040 1045 1050

Ser Gly Asn Ser Arg Pro Arg Val Arg Ala Pro Phe Pro Gln Asp
1055 1060 1065

Trp Val Pro Glu Glu Lys Glu Val Pro Asn Ile Ser Gln Pro Pro
1070 1075 1080

Gln Val Pro Pro Ser Pro Trp Val Arg Ser Arg Arg Pro Lys Arg
1085 1090 1095

Val Leu Pro Cys Gln Leu Gln Ser Gly Gly Ala Val Pro Gly Gly
1100 1105 1110

Lys Lys Gly Cys Gln Gly Pro Val Thr Lys Ser Leu Gly Phe Val
1115 1120 1125

Val Pro Thr Cys Cys Cys His His Gln Thr Gln Ser Phe Phe Ser
1130 1135 1140

Leu Val Asn Ala Pro Pro Pro Ala Ala Ala Phe Ile Leu Lys Val
1145 1150 1155

Phe Glu Phe Cys Phe Trp Ser Phe Phe Ser Pro Phe Pro Phe Cys
1160 1165 1170

Phe Phe Val Leu Phe Phe Tyr Arg Pro Cys His Asn Phe Val Leu
1175 1180 1185

Glu Gly Thr Cys Phe Thr Met Ala Ser Phe Ala Gln Val Glu Thr
1190 1195 1200

Gly Ala His His His Val Cys Phe Gln Asn Ser Ala Leu Val Ile
1205 1210 1215

Pro His Pro Arg Thr Pro Pro Gly Thr Pro Lys Leu Cys Pro Met
1220 1225 1230

Lys Gly Cys Gly Val Arg Lys Gly Arg Leu Val Val Glu Pro Arg
1235 1240 1245

Asn Gly Arg Arg Cys Leu Glu Gly Phe Leu Asn Tyr Ile Lys Ser
1250 1255 1260

Asn Phe Leu Tyr Lys Lys Lys Met Gly Arg Val Pro Ala Pro Gly
1265 1270 1275

Val
1276

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser
1 5 10 15

Asp Phe Gly Leu Ser Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro
20 25 30

Thr Tyr Thr Ser Ala Leu Gly Gly Lys Ile Pro Met Arg Trp Thr
35 40 45

Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Ala Ser Ala Ser
50 55 59

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
1 5 10 15

Gly Leu Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala
20 25 30

Asp Gly Gly Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile
35 40 45

His Tyr Arg Lys Phe Thr His Gln Ser
50 54

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Asn Cys Met Leu Ala Gly Asp Met Thr Val Cys Val Ala Asp Phe
1 5 10 15

Gly Leu Ser Trp Lys Ile Tyr Ser Gly Ala Thr Ile Val Arg Gly
20 25 30

Cys Ala Ser Lys Leu Pro Val Lys Trp Leu Ala Leu Gly Ser Leu
35 40 45

Ala Asp Asn Leu Tyr Thr Val His Ser
50 54

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Asn Cys Leu Val Gly Lys Asn Tyr Thr Ile Lys Ile Ala Asp Phe
1 5 10 15

Gly Met Ser Arg Asn Leu Tyr Ser Gly Asp Tyr Tyr
20 25 27

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Thr Arg Asn Ile Leu Val Glu Asn Glu Asn Arg Val Lys Ile Gly
1 5 10 15

Asp Phe Gly Leu Thr Lys Val Leu Pro Gln Asp Lys Glu Tyr Tyr
20 25 30

Lys Val Lys Glu Pro Gly Glu Ser Pro Ile Phe Trp Tyr Ala Pro
35 40 45

Glu Ser Leu Thr Glu Ser Leu Phe Ser Val Ala Ser Asp
50 55 58

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser
1 5 10 15

Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala
20 25 30

Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro
35 40 45

Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp
50 55 58

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4425 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TCGGGTCGGA CCCACGCGCA GCGGCCGGAG ATGCAGCGGG GCGCCGCGCT 50

GTGCCTGCGA CTGTGGCTCT GCCTGGGACT CCTGGACGGC CTGGTGAGTG 100

GCTACTCCAT GACCCCCCCG ACCTTGAACA TCACGGAGGA GTCACACGTC 150

ATCGACACCG GTGACAGCCT GTCCATCTCC TGCAGGGGAC AGCACCCCCT 200

CGAGTGGGCT TGGCCAGGAG CTCAGGAGGC GCCAGCCACC GGAGACAAGG 250

ACAGCGAGGA CACGGGGGTG GTGCGAGACT GCGAGGGCAC AGACGCCAGG 300

CCCTACTGCA AGGTGTTGCT GCTGCACGAG GTACATGCCA ACGACACAGG 350

CAGCTACGTC TGCTACTACA AGTACATCAA GGCACGCATC GAGGGCACCA 400

CGGCCGCCAG CTCCTACGTG TTCGTGAGAG ACTTTGAGCA GCCATTCATC 450

AACAAGCCTG ACACGCTCTT GGTCAACAGG AAGGACGCCA TGTGGGTGCC 500

CTGTCTGGTG TCCATCCCCG GCCTCAATGT CACGCTGCGC TCGCAAAGCT 550

CGGTGCTGTG GCCAGACGGG CAGGAGGTGG TGTGGGATGA CCGGCGGGGC 600

ATGCTCGTGT CCACGCCACT GCTGCACGAT GCCCTGTACC TGCAGTGCGA 650

GACCACCTGG GGAGACCAGG ACTTCCTTTC CAACCCCTTC CTGGTGCACA 700

TCACAGGCAA CGAGCTCTAT GACATCCAGC TGTTGCCCAG GAAGTCGCTG 750

GAGCTGCTGG TAGGGGAGAA GCTGGTCCTG AACTGCACCG TGTGGGCTGA 800

GTTTAACTCA GGTGTCACCT TTGACTGGGA CTACCCAGGG AAGCAGGCAG 850

AGCGGGGTAA GTGGGTGCCC GAGCGACGCT CCCAGCAGAC CCACACAGAA 900

CTCTCCAGCA TCCTGACCAT CCACAACGTC AGCCAGCACG ACCTGGGCTC 950

GTATGTGTGC AAGGCCAACA ACGGCATCCA GCGATTTCGG GAGAGCACCG 1000

AGGTCATTGT GCATGAAAAT CCCTTCATCA GCGTCGAGTG GCTCAAAGGA 1050

CCCATCCTGG AGGCCACGGC AGGAGACGAG CTGGTGAAGC TGCCCGTGAA 1100

GCTGGCAGCG TACCCCCCGC CCGAGTTCCA GTGGTACAAG GATGGAAAGG 1150

CACTGTCCGG GCGCCACAGT CCACATGCCC TGGTGCTCAA GGAGGTGACA 1200

GAGGCCAGCA CAGGCACCTA CACCCTCGCC CTGTGGAACT CCGCTGCTGG 1250

CCTGAGGCGC AACATCAGCC TGGAGCTGGT GGTGAATGTG CCCCCCCAGA 1300

TACATGAGAA GGAGGCCTCC TCCCCCAGCA TCTACTCGCG TCACAGCCGC 1350

CAGGCCCTCA CCTGCACGGC CTACGGGGTG CCCCTGCCTC TCAGCATCCA 1400

GTGGCACTGG CGGCCCTGGA CACCCTGCAA GATGTTTGCC CAGCGTAGTC 1450

TCCGGCGGCG GCAGCAGCAA GACCTCATGC CACAGTGCCG TGACTGGAGG 1500

GCGGTGACCA CGCAGGATGC CGTGAACCCC ATCGAGAGCC TGGACACCTG 1550

GACCGAGTTT GTGGAGGGAA AGAATAAGAC TGTGAGCAAG CTGGTGATCC 1600

AGAATGCCAA CGTGTCTGCC ATGTACAAGT GTGTGGTCTC CAACAAGGTG 1650

GGCCAGGATG AGCGGCTCAT CTACTTCTAT GTGACCACCA TCCCCGACGG 1700

CTTCACCATC GAATCCAAGC CATCCGAGGA GCTACTAGAG GGCCAGCCGG 1750

TGCTCCTGAG CTGCCAAGCC GACAGCTACA AGTACGAGCA TCTGCGCTGG 1800

TACCGCCTCA ACCTGTCCAC GCTGCACGAT GCGCACGGGA ACCCGCTTCT 1850

GCTCGACTGC AAGAACGTGC ATCTGTTCGC CACCCCTCTG GCCGCCAGCC 1900

TGGAGGAGGT GGCACCTGGG GCGCGCCACG CCACGCTCAG CCTGAGTATC 1950

CCCCGCGTCG CGCCCGAGCA CGAGGGCCAC TATGTGTGCG AAGTGCAAGA 2000

CCGGCGCAGC CATGACAAGC ACTGCCACAA GAAGTACCTG TCGGTGCAGG 2050

CCCTGGAAGC CCCTCGGCTC ACGCAGAACT TGACCGACCT CCTGGTGAAC 2100

GTGAGCGACT CGCTGGAGAT GCAGTGCTTG GTGGCCGGAG CGCACGCGCC 2150

CAGCATCGTG TGGTACAAAG ACGAGAGGCT GCTGGAGGAA AAGTCTGGAG 2200

TCGACTTGGC GGACTCCAAC CAGAAGCTGA GCATCCAGCG CGTGCGCGAG 2250

GAGGATGCGG GACGCTATCT GTGCAGCGTG TGCAACGCCA AGGGCTGCGT 2300

CAACTCCTCC GCCAGCGTGG CCGTGGAAGG CTCCGAGGAT AAGGGCAGCA 2350

TGGAGATCGT GATCCTTGTC GGTACCGGCG TCATCGCTGT CTTCTTCTGG 2400

GTCCTCCTCC TCCTCATCTT CTGTAACATG AGGAGGCCGG CCCACGCAGA 2450

CATCAAGACG GGCTACCTGT CCATCATCAT GGACCCCGGG GAGGTGCCTC 2500

TGGAGGAGCA ATGCGAATAC CTGTCCTACG ATGCCAGCCA GTGGGAATTC 2550

CCCCGAGAGC GGCTGCACCT GGGGAGAGTG CTCGGCTACG GCGCCTTCGG 2600

GAAGGTGGTG GAAGCCTCCG CTTTCGGCAT CCACAAGGGC AGCAGCTGTG 2650

ACACCGTGGC CGTGAAAATG CTGAAAGAGG GCGCCACGGC CAGCGAGCAC 2700

CGCGCGCTGA TGTCGGAGCT CAAGATCCTC ATTCACATCG GCAACCACCT 2750

CAACGTGGTC AACCTCCTCG GGGCGTGCAC CAAGCCGCAG GGCCCCCTCA 2800

TGGTGATCGT GGAGTTCTGC AAGTACGGCA ACCTCTCCAA CTTCCTGCGC 2850

GCCAAGCGGG ACGCCTTCAG CCCCTGCGCG GAGAAGTCTC CCGAGCAGCG 2900

CGGACGCTTC CGCGCCATGG TGGAGCTCGC CAGGCTGGAT CGGAGGCGGC 2950

CGGGGAGCAG CGACAGGGTC CTCTTCGCGC GGTTCTCGAA GACCGAGGGC 3000

GGAGCGAGGC GGGCTTCTCC AGACCAAGAA GCTGAGGACC TGTGGCTGAG 3050

CCCGCTGACC ATGGAAGATC TTGTCTGCTA CAGCTTCCAG GTGGCCAGAG 3100

GGATGGAGTT CCTGGCTTCC CGAAAGTGCA TCCACAGAGA CCTGGCTGCT 3150

CGGAACATTC TGCTGTCGGA AAGCGACGTG GTGAAGATCT GTGACTTTGG 3200

CCTTGCCCGG GACATCTACA AAGACCCTGA CTACGTCCGC AAGGGCAGTG 3250

CCCGGCTGCC CCTGAAGTGG ATGGCCCCTG AAAGCATCTT CGACAAGGTG 3300

TACACCACGC AGAGTGACGT GTGGTCCTTT GGGGTGCTTC TCTGGGAGAT 3350

CTTCTCTCTG GGGGCCTCCC CGTACCCTGG GGTGCAGATC AATGAGGAGT 3400

TCTGCCAGCG GCTGAGAGAC GGCACAAGGA TGAGGGCCCC GGAGCTGGCC 3450

ACTCCCGCCA TACGCCGCAT CATGCTGAAC TGCTGGTCCG GAGACCCCAA 3500

GGCGAGACCT GCATTCTCGG AGCTGGTGGA GATCCTGGGG GACCTGCTCC 3550

AGGGCAGGGG CCTGCAAGAG GAAGAGGAGG TCTGCATGGC CCCGCGCAGC 3600

TCTCAGAGCT CAGAAGAGGG CAGCTTCTCG CAGGTGTCCA CCATGGCCCT 3650

ACACATCGCC CAGGCTGACG CTGAGGACAG CCCGCCAAGC CTGCAGCGCC 3700

ACAGCCTGGC CGCCAGGTAT TACAACTGGG TGTCCTTTCC CGGGTGCCTG 3750

GCCAGAGGGG CTGAGACCCG TGGTTCCTCC AGGATGAAGA CATTTGAGGA 3800

ATTCCCCATG ACCCCAACGA CCTACAAAGG CTCTGTGGAC AACCAGACAG 3850

ACAGTGGGAT GGTGCTGGCC TCGGAGGAGT TTGAGCAGAT AGAGAGCAGG 3900

CATAGACAAG AAAGCGGCTT CAGGTAGCTG AAGCAGAGAG AGAGAAGGCA 3950

GCATACGTCA GCATTTTCTT CTCTGCACTT ATAAGAAAGA TCAAAGACTT 4000

TAAGACTTTC GCTATTTCTT CTGCTATCTA CTACAAACTT CAAAGAGGAA 4050

CCAGGAGGCC AAGAGGAGCA TGAAAGTGGA CAAGGAGTGT GACCACTGAA 4100

GCACCACAGG GAGGGGTTAG GCCTCCGGAT GACTGCGGGC AGGCCTGGAT 4150

AATATCCAGC CTCCCACAAG AAGCTGGTGG AGCAGAGTGT TCCCTGACTC 4200

CTCCAAGGAA AGGGAGACGC CCTTTCATGG TCTGCTGAGT AACAGGTGCC 4250

TTCCCAGACA CTGGCGTTAC TGCTTGACCA AAGAGCCCTC AAGCGGCCCT 4300

TATGCCAGCG TGACAGAGGG CTCACCTCTT GCCTTCTAGG TCACTTCTCA 4350

CAATGTCCCT TCAGCACCTG ACCCTGTGCC CGCCAGTTAT TCCTTGGTAA 4400

TATGAGTAAT ACATCAAAGA GTAGT 4425

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4425 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

AGCCCAGCCT GGGTGCGCGT CGCCGGCCTC TACGTCGCCC CGCGGCGCGA 50

CACGGACGCT GACACCGAGA CGGACCCTGA GGACCTGCCG GACCACTCAC 100

CGATGAGGTA CTGGGGGGGC TGGAACTTGT AGTGCCTCCT CAGTGTGCAG 150

TAGCTGTGGC CACTGTCGGA CAGGTAGAGG ACGTCCCCTG TCGTGGGGGA 200

GCTCACCCGA ACCGGTCCTC GAGTCCTCCG CGGTCGGTGG CCTCTGTTCC 250

TGTCGCTCCT GTGCCCCCAC CACGCTCTGA CGCTCCCGTG TCTGCGGTCC 300

GGGATGACGT TCCACAACGA CGACGTGCTC CATGTACGGT TGCTGTGTCC 350

GTCGATGCAG ACGATGATGT TCATGTAGTT CCGTGCGTAG CTCCCGTGGT 400

GCCGGCGGTC GAGGATGCAC AAGCACTCTC TGAAACTCGT CGGTAAGTAG 450

TTGTTCGGAC TGTGCGAGAA CCAGTTGTCC TTCCTGCGGT ACACCCACGG 500

GACAGACCAC AGGTAGGGGC CGGAGTTACA GTGCGACGCG AGCGTTTCGA 550

GCCACGACAC CGGTCTGCCC GTCCTCCACC ACACCCTACT GGCCGCCCCG 600

TACGAGCACA GGTGCGGTGA CGACGTGCTA CGGGACATGG ACGTCACGCT 650

CTGGTGGACC CCTCTGGTCC TGAAGGAAAG GTTGGGGAAG GACCACGTGT 700

AGTGTCCGTT GCTCGAGATA CTGTAGGTCG ACAACGGGTC CTTCAGCGAC 750

CTCGACGACC ATCCCCTCTT CGACCAGGAC TTGACGTGGC ACACCCGACT 800

CAAATTGAGT CCACAGTGGA AACTGACCCT GATGGGTCCC TTCGTCCGTC 850

TCGCCCCATT CACCCACGGG CTCGCTGCGA GGGTCGTCTG GGTGTGTCTT 900

GAGAGGTCGT AGGACTGGTA GGTGTTGCAG TCGGTCGTGC TGGACCCGAG 950

CATACACACG TTCCGGTTGT TGCCGTAGGT CGCTAAAGCC CTCTCGTGGC 1000

TCCAGTAACA CGTACTTTTA GGGAAGTAGT CGCAGCTCAC CGAGTTTCCT 1050

GGGTAGGACC TCCGGTGCCG TCCTCTGCTC GACCACTTCG ACGGGCACTT 1100

CGACCGTCGC ATGGGGGGCG GGCTCAAGGT CACCATGTTC CTACCTTTCC 1150

GTGACAGGCC CGCGGTGTCA GGTGTACGGG ACCACGAGTT CCTCCACTGT 1200

CTCCGGTCGT GTCCGTGGAT GTGGGAGCGG GACACCTTGA GGCGACGACC 1250

GGACTCCGCG TTGTAGTCGG ACCTCGACCA CCACTTACAC GGGGGGGTCT 1300

ATGTACTCTT CCTCCGGAGG AGGGGGTCGT AGATGAGCGC AGTGTCGGCG 1350

GTCCGGGAGT GGACGTGCCG GATGCCCCAC GGGGACGGAG AGTCGTAGGT 1400

CACCGTGACC GCCGGGACCT GTGGGACGTT CTACAAACGG GTCGCATCAG 1450

AGGCCGCCGC CGTCGTCGTT CTGGAGTACG GTGTCACGGC ACTGACCTCC 1500

CGCCACTGGT GCGTCCTACG GCACTTGGGG TAGCTCTCGG ACCTGTGGAC 1550

CTGGCTCAAA CACCTCCCTT TCTTATTCTG ACACTCGTTC GACCACTAGG 1600

TCTTACGGTT GCACAGACGG TACATGTTCA CACACCAGAG GTTGTTCCAC 1650

CCGGTCCTAC TCGCCGAGTA GATGAAGATA CACTGGTGGT AGGGGCTGCC 1700

GAAGTGGTAG CTTAGGTTCG GTAGGCTCCT CGATGATCTC CCGGTCGGCC 1750

ACGAGGACTC GACGGTTCGG CTGTCGATGT TCATGCTCGT AGACGCGACC 1800

ATGGCGGAGT TGGACAGGTG CGACGTGCTA CGCGTGCCCT TGGGCGAAGA 1850

CGAGCTGACG TTCTTGCACG TAGACAAGCG GTGGGGAGAC CGGCGGTCGG 1900

ACCTCCTCCA CCGTGGACCC CGCGCGGTGC GGTGCGAGTC GGACTCATAG 1950

GGGGCGCAGC GCGGGCTCGT GCTCCCGGTG ATACACACGC TTCACGTTCT 2000

GGCCGCGTCG GTACTGTTCG TGACGGTGTT CTTCATGGAC AGCCACGTCC 2050

GGGACCTTCG GGGAGCCGAG TGCGTCTTGA ACTGGCTGGA GGACCACTTG 2100

CACTCGCTGA GCGACCTCTA CGTCACGAAC CACCGGCCTC GCGTGCGCGG 2150

GTCGTAGCAC ACCATGTTTC TGCTCTCCGA CGACCTCCTT TTCAGACCTC 2200

AGCTGAACCG CCTGAGGTTG GTCTTCGACT CGTAGGTCGC GCACGCGCTC 2250

CTCCTACGCC CTGCGATAGA CACGTCGCAC ACGTTGCGGT TCCCGACGCA 2300

GTTGAGGAGG CGGTCGCACC GGCACCTTCC GAGGCTCCTA TTCCCGTCGT 2350

ACCTCTAGCA CTAGGAACAG CCATGGCCGC AGTAGCGACA GAAGAAGACC 2400

CAGGAGGAGG AGGAGTAGAA GACATTGTAC TCCTCCGGCC GGGTGCGTCT 2450

GTAGTTCTGC CCGATGGACA GGTAGTAGTA CCTGGGGCCC CTCCACGGAG 2500

ACCTCCTCGT TACGCTTATG GACAGGATGC TACGGTCGGT CACCCTTAAG 2550

GGGGCTCTCG CCGACGTGGA CCCCTCTCAC GAGCCGATGC CGCGGAAGCC 2600

CTTCCACCAC CTTCGGAGGC GAAAGCCGTA GGTGTTCCCG TCGTCGACAC 2650

TGTGGCACCG GCACTTTTAC GACTTTCTCC CGCGGTGCCG GTCGCTCGTG 2700

GCGCGCGACT ACAGCCTCGA GTTCTAGGAG TAAGTGTAGC CGTTGGTGGA 2750

GTTGCACCAG TTGGAGGAGC CCCGCACGTG GTTCGGCGTC CCGGGGGAGT 2800

ACCACTAGCA CCTCAAGACG TTCATGCCGT TGGAGAGGTT GAAGGACGCG 2850

CGGTTCGCCC TGCGGAAGTC GGGGACGCGC CTCTTCAGAG GGCTCGTCGC 2900

GCCTGCGAAG GCGCGGTACC ACCTCGAGCG GTCCGACCTA GCCTCCGCCG 2950

GCCCCTCGTC GCTGTCCCAG GAGAAGCGCG CCAAGAGCTT CTGGCTCCCG 3000

CCTCGCTCCG CCCGAAGAGG TCTGGTTCTT CGACTCCTGG ACACCGACTC 3050

GGGCGACTGG TACCTTCTAG AACAGACGAT GTCGAAGGTC CACCGGTCTC 3100

CCTACCTCAA GGACCGAAGG GCTTTCACGT AGGTGTCTCT GGACCGACGA 3150

GCCTTGTAAG ACGACAGCCT TTCGCTGCAC CACTTCTAGA CACTGAAACC 3200

GGAACGGGCC CTGTAGATGT TTCTGGGACT GATGCAGGCG TTCCCGTCAC 3250

GGGCCGACGG GGACTTCACC TACCGGGGAC TTTCGTAGAA GCTGTTCCAC 3300

ATGTGGTGCG TCTCACTGCA CACCAGGAAA CCCCACGAAG AGACCCTCTA 3350

GAAGAGAGAC CCCCGGAGGG GCATGGGACC CCACGTCTAG TTACTCCTCA 3400

AGACGGTCGC CGACTCTCTG CCGTGTTCCT ACTCCCGGGG CCTCGACCGG 3450

TGAGGGCGGT ATGCGGCGTA GTACGACTTG ACGACCAGGC CTCTGGGGTT 3500

CCGCTCTGGA CGTAAGAGCC TCGACCACCT CTAGGACCCC CTGGACGAGG 3550

TCCCGTCCCC GGACGTTCTC CTTCTCCTCC AGACGTACCG GGGCGCGTCG 3600

AGAGTCTCGA GTCTTCTCCC GTCGAAGAGC GTCCACAGGT GGTACCGGGA 3650

TGTGTAGCGG GTCCGACTGC GACTCCTGTC GGGCGGTTCG GACGTCGCGG 3700

TGTCGGACCG GCGGTCCATA ATGTTGACCC ACAGGAAAGG GCCCACGGAC 3750

CGGTCTCCCC GACTCTGGGC ACCAAGGAGG TCCTACTTCT GTAAACTCCT 3800

TAAGGGGTAC TGGGGTTGCT GGATGTTTCC GAGACACCTG TTGGTCTGTC 3850

TGTCACCCTA CCACGACCGG AGCCTCCTCA AACTCGTCTA TCTCTCGTCC 3900

GTATCTGTTC TTTCGCCGAA GTCCATCGAC TTCGTCTCTC TCTCTTCCGT 3950

CGTATGCAGT CGTAAAAGAA GAGACGTGAA TATTCTTTCT AGTTTCTGAA 4000

ATTCTGAAAG CGATAAAGAA GACGATAGAT GATGTTTGAA GTTTCTCCTT 4050

GGTCCTCCGG TTCTCCTCGT ACTTTCACCT GTTCCTCACA CTGGTGACTT 4100

CGTGGTGTCC CTCCCCAATC CGGAGGCCTA CTGACGCCCG TCCGGACCTA 4150

TTATAGGTCG GAGGGTGTTC TTCGACCACC TCGTCTCACA AGGGACTGAG 4200

GAGGTTCCTT TCCCTCTGCG GGAAAGTACC AGACGACTCA TTGTCCACGG 4250

AAGGGTCTGT GACCGCAATG ACGAACTGGT TTCTCGGGAG TTCGCCGGGA 4300

ATACGGTCGC ACTGTCTCCC GAGTGGAGAA CGGAAGATCC AGTGAAGAGT 4350

GTTACAGGGA AGTCGTGGAC TGGGACACGG GCGGTCAATA AGGAACCATT 4400

ATACTCATTA TGTAGTTTCT CATCA 4425

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1298 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu
1 5 10 15

Gly Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr Pro Pro
20 25 30

Thr Leu Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp
35 40 45

Ser Leu Ser Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala
50 55 60

Trp Pro Gly Ala Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser
65 70 75

Glu Asp Thr Gly Val Val Arg Asp Cys Glu Gly Thr Asp Ala Arg
80 85 90

Pro Tyr Cys Lys Val Leu Leu Leu His Glu Val His Ala Asn Asp
95 100 105

Thr Gly Ser Tyr Val Cys Tyr Tyr Lys Tyr Ile Lys Ala Arg Ile
110 115 120

Glu Gly Thr Thr Ala Ala Ser Ser Tyr Val Phe Val Arg Asp Phe
125 130 135

Glu Gln Pro Phe Ile Asn Lys Pro Asp Thr Leu Leu Val Asn Arg
140 145 150

Lys Asp Ala Met Trp Val Pro Cys Leu Val Ser Ile Pro Gly Leu
155 160 165

Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu Trp Pro Asp Gly
170 175 180

Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu Val Ser Thr
185 190 195

Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr Thr Trp
200 205 210

Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile Thr
215 220 225

Gly Asn Glu Leu Tyr Asp Ile Gln Leu Leu Pro Arg Lys Ser Leu
230 235 240

Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn Cys Thr Val Trp
245 250 255

Ala Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp Tyr Pro Gly
260 265 270

Lys Gln Ala Glu Arg Gly Lys Trp Val Pro Glu Arg Arg Ser Gln
275 280 285

Gln Thr His Thr Glu Leu Ser Ser Ile Leu Thr Ile His Asn Val
290 295 300

Ser Gln His Asp Leu Gly Ser Tyr Val Cys Lys Ala Asn Asn Gly
305 310 315

Ile Gln Arg Phe Arg Glu Ser Thr Glu Val Ile Val His Glu Asn
320 325 330

Pro Phe Ile Ser Val Glu Trp Leu Lys Gly Pro Ile Leu Glu Ala
335 340 345

Thr Ala Gly Asp Glu Leu Val Lys Leu Pro Val Lys Leu Ala Ala
350 355 360

Tyr Pro Pro Pro Glu Phe Gln Trp Tyr Lys Asp Gly Lys Ala Leu
365 370 375

Ser Gly Arg His Ser Pro His Ala Leu Val Leu Lys Glu Val Thr
380 385 390

Glu Ala Ser Thr Gly Thr Tyr Thr Leu Ala Leu Trp Asn Ser Ala
395 400 405

Ala Gly Leu Arg Arg Asn Ile Ser Leu Glu Leu Val Val Asn Val
410 415 420

Pro Pro Gln Ile His Glu Lys Glu Ala Ser Ser Pro Ser Ile Tyr
425 430 435

Ser Arg His Ser Arg Gln Ala Leu Thr Cys Thr Ala Tyr Gly Val
440 445 450

Pro Leu Pro Leu Ser Ile Gln Trp His Trp Arg Pro Trp Thr Pro
455 460 465

Cys Lys Met Phe Ala Gln Arg Ser Leu Arg Arg Arg Gln Gln Gln
470 475 480

Asp Leu Met Pro Gln Cys Arg Asp Trp Arg Ala Val Thr Thr Gln
485 490 495

Asp Ala Val Asn Pro Ile Glu Ser Leu Asp Thr Trp Thr Glu Phe
500 505 510

Val Glu Gly Lys Asn Lys Thr Val Ser Lys Leu Val Ile Gln Asn
515 520 525

Ala Asn Val Ser Ala Met Tyr Lys Cys Val Val Ser Asn Lys Val
530 535 540

Gly Gln Asp Glu Arg Leu Ile Tyr Phe Tyr Val Thr Thr Ile Pro
545 550 555

Asp Gly Phe Thr Ile Glu Ser Lys Pro Ser Glu Glu Leu Leu Glu
560 565 570

Gly Gln Pro Val Leu Leu Ser Cys Gln Ala Asp Ser Tyr Lys Tyr
575 580 585

Glu His Leu Arg Trp Tyr Arg Leu Asn Leu Ser Thr Leu His Asp
590 595 600

Ala His Gly Asn Pro Leu Leu Leu Asp Cys Lys Asn Val His Leu
605 610 615

Phe Ala Thr Pro Leu Ala Ala Ser Leu Glu Glu Val Ala Pro Gly
620 625 630

Ala Arg His Ala Thr Leu Ser Leu Ser Ile Pro Arg Val Ala Pro
635 640 645

Glu His Glu Gly His Tyr Val Cys Glu Val Gln Asp Arg Arg Ser
650 655 660

His Asp Lys His Cys His Lys Lys Tyr Leu Ser Val Gln Ala Leu
665 670 675

Glu Ala Pro Arg Leu Thr Gln Asn Leu Thr Asp Leu Leu Val Asn
680 685 690

Val Ser Asp Ser Leu Glu Met Gln Cys Leu Val Ala Gly Ala His
695 700 705

Ala Pro Ser Ile Val Trp Tyr Lys Asp Glu Arg Leu Leu Glu Glu
710 715 720

Lys Ser Gly Val Asp Leu Ala Asp Ser Asn Gln Lys Leu Ser Ile
725 730 735

Gln Arg Val Arg Glu Glu Asp Ala Gly Arg Tyr Leu Cys Ser Val
740 745 750

Cys Asn Ala Lys Gly Cys Val Asn Ser Ser Ala Ser Val Ala Val
755 760 765

Glu Gly Ser Glu Asp Lys Gly Ser Met Glu Ile Val Ile Leu Val
770 775 780

Gly Thr Gly Val Ile Ala Val Phe Phe Trp Val Leu Leu Leu Leu
785 790 795

Ile Phe Cys Asn Met Arg Arg Pro Ala His Ala Asp Ile Lys Thr
800 805 810

Gly Tyr Leu Ser Ile Ile Met Asp Pro Gly Glu Val Pro Leu Glu
815 820 825

Glu Gln Cys Glu Tyr Leu Ser Tyr Asp Ala Ser Gln Trp Glu Phe
830 835 840

Pro Arg Glu Arg Leu His Leu Gly Arg Val Leu Gly Tyr Gly Ala
845 850 855

Phe Gly Lys Val Val Glu Ala Ser Ala Phe Gly Ile His Lys Gly
860 865 870

Ser Ser Cys Asp Thr Val Ala Val Lys Met Leu Lys Glu Gly Ala
875 880 885

Thr Ala Ser Glu His Arg Ala Leu Met Ser Glu Leu Lys Ile Leu
890 895 900

Ile His Ile Gly Asn His Leu Asn Val Val Asn Leu Leu Gly Ala
905 910 915

Cys Thr Lys Pro Gln Gly Pro Leu Met Val Ile Val Glu Phe Cys
920 925 930

Lys Tyr Gly Asn Leu Ser Asn Phe Leu Arg Ala Lys Arg Asp Ala
935 940 945

Phe Ser Pro Cys Ala Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe
950 955 960

Arg Ala Met Val Glu Leu Ala Arg Leu Asp Arg Arg Arg Pro Gly
965 970 975

Ser Ser Asp Arg Val Leu Phe Ala Arg Phe Ser Lys Thr Glu Gly
980 985 990

Gly Ala Arg Arg Ala Ser Pro Asp Gln Glu Ala Glu Asp Leu Trp
995 1000 1005

Leu Ser Pro Leu Thr Met Glu Asp Leu Val Cys Tyr Ser Phe Gln
1010 1015 1020

Val Ala Arg Gly Met Glu Phe Leu Ala Ser Arg Lys Cys Ile His
1025 1030 1035

Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Ser Asp Val
1040 1045 1050

Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp
1055 1060 1065

Pro Asp Tyr Val Arg Lys Gly Ser Ala Arg Leu Pro Leu Lys Trp
1070 1075 1080

Met Ala Pro Glu Ser Ile Phe Asp Lys Val Tyr Thr Thr Gln Ser
1085 1090 1095

Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu
1100 1105 1110

Gly Ala Ser Pro Tyr Pro Gly Val Gln Ile Asn Glu Glu Phe Cys
1115 1120 1125

Gln Arg Leu Arg Asp Gly Thr Arg Met Arg Ala Pro Glu Leu Ala
1130 1135 1140

Thr Pro Ala Ile Arg Arg Ile Met Leu Asn Cys Trp Ser Gly Asp
1145 1150 1155

Pro Lys Ala Arg Pro Ala Phe Ser Glu Leu Val Glu Ile Leu Gly
1160 1165 1170

Asp Leu Leu Gln Gly Arg Gly Leu Gln Glu Glu Glu Glu Val Cys
1175 1180 1185

Met Ala Pro Arg Ser Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser
1190 1195 1200

Gln Val Ser Thr Met Ala Leu His Ile Ala Gln Ala Asp Ala Glu
1205 1210 1215

Asp Ser Pro Pro Ser Leu Gln Arg His Ser Leu Ala Ala Arg Tyr
1220 1225 1230

Tyr Asn Trp Val Ser Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu
1235 1240 1245

Thr Arg Gly Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro Met
1250 1255 1260

Thr Pro Thr Thr Tyr Lys Gly Ser Val Asp Asn Gln Thr Asp Ser
1265 1270 1275

Gly Met Val Leu Ala Ser Glu Glu Phe Glu Gln Ile Glu Ser Arg
1280 1285 1290

His Arg Gln Glu Ser Gly Phe Arg
1295 1298

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3348 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATGGCTGGGA TTTTCTATTT CGCCCTATTT TCGTGTCTCT TCGGGATTTG 50

CGACGCTGTC ACAGGTTCCA GGGTATACCC CGCGAATGAA GTTACCTTAT 100

TGGATTCCAG ATCTGTTCAG GGAGAACTTG GGTGGATAGC AAGCCCTCTG 150

GAAGGAGGGT GGGAGGAAGT GAGTATCATG GATGAAAAAA ATACACCAAT 200

CCGAACCTAC CAAGTGTGCA ATGTGATGGA ACCCAGCCAG AATAACTGGC 250

TACGAACTGA TTGGATCACC CGAGAAGGGG CTCAGAGGGT GTATATTGAG 300

ATTAAATTCA CCTTGAGGGA CTGCAATAGT CTTCCGGGCG TCATGGGGAC 350

TTGCAAGGAG ACGTTTAACC TGTACTACTA TGAATCAGAC AACGACAAAG 400

AGCGTTTCAT CAGAGAGAAC CAGTTTGTCA AAATTGACAC CATTGCTGCT 450